Exhibit 34

Masonic Cancer Center
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Comprehensive Cancer Center designated by the National Cancer Institute

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Adam M. Slater
Mazie Slater Katz & Freeman
103 Eisenhower Parkway
Roseland, New Jersey 07068

Dear Mr. Slater:

At your request I have reviewed scientific literature, corporate documents, deposition testimony, and regulatory documents and standards, as set forth in this report and the attached Exhibits, and applied my education, training, and knowledge to provide opinions related to the contamination of valsartan manufactured by API manufacturers including ZHP, Hetero, Mylan, and Aurobindo with nitrosamines, and in particular NDMA and NDEA (the "contaminated valsartan"), and then incorporated into finished dose form by the same manufacturers, as well as finished dose manufacturers Teva and Torrent, who purchased the API from the API manufacturers (Teva from ZHP and Mylan, Torrent from ZHP) and incorporated the contaminated valsartan into their finished doses.

As set forth in detail herein, it is my opinion that the NDMA and NDEA levels found in the contaminated valsartan were completely avoidable and therefore are and were unreasonably dangerous, causing an increased risk for the development of cancer for those people ingesting the contaminated valsartan. All opinions set forth herein are held to a reasonable degree of scientific certainty, and have been formed based upon application of scientifically validated methodologies that I utilize in my own scientific work. My background and credentials are set forth in my curriculum vitae, which is attached hereto as Exhibit 1. The list of documents reviewed as part of my analysis is attached hereto as Exhibit 2. The list of scientific literature references specifically relied on for my opinions is attached hereto as Exhibit 3, with the caveat that the scientific literature relevant to the issues addressed is vast, and my familiarity with that literature certainly informs my knowledge in this field, as does all of my experience, even if not specifically listed.

Stephen S. Hecht

Stephen S. Hecht, Ph.D.
Wallin Professor of Cancer Prevention
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I. Professional Background

I will first provide an overview of my professional background. I received my B.S. degree in chemistry (with honors) from Duke University in 1964 and my Ph.D. in organic chemistry from the Massachusetts Institute of Technology (MIT) in 1968. From 1968-69, I held a postdoctoral fellowship position at MIT in the laboratory of Professor Klaus Biemann, a pioneer in the application of mass spectrometry to organic chemical analysis. My research helped lay the groundwork for analysis of samples to be returned by NASA astronauts from the moon, and analyzed for trace organic molecules using mass spectrometry. I was an assistant professor of chemistry at Haverford College from 1969-1971, and a National Research Council Fellow at the U.S. Department of Agriculture from 1971-1973, carrying out research on practical applications for utilizing excess animal fat. My research career on nitrosamines began when I joined the American Health Foundation in 1973, initially as Head of the Section of Organic Chemistry in the Division of Environmental Carcinogenesis (1973-1980), then as Head of the Division of Chemical Carcinogenesis (1980-1996), and concurrently as Director of Research for the Foundation (1987-1996). The American Health Foundation was a private research institute founded by the eminent epidemiologist Ernst L. Wynder. I will discuss my research in more detail later, but I note here that I have carried out research related to nitrosamines continually since 1973. I have been continually funded for this research by the U.S. National Cancer Institute since 1975. Among a number of highly important contributions to the nitrosamine research field, my colleagues and I were the first to characterize "tobacco-specific nitrosamines" in tobacco products. These nitrosamines, among which are the powerful cancer causing agents NNK (Nicotine-derived nitrosamine ketone) and NNN (*N*-Nitrosonornicotine), considered "carcinogenic to humans" by the International Agency for Research on Cancer, are widely viewed as some of the main cancer causing agents in tobacco products. Our research paper in the 1978 Journal of the National Cancer Institute, describing these compounds, has been cited by the American Association for Cancer Research as a "Landmark in Cancer Research." In 1996, I relocated to the University of Minnesota where I hold my current position as Wallin Professor of Cancer Prevention, a "Land Grant Endowed Chair" in cancer prevention research. My academic appointment is in the Department of Laboratory Medicine and Pathology, in the University of Minnesota Medical School. I am also a member of the Medicinal Chemistry and Pharmacology graduate programs. From 1998-2014, I was the founding Head of the Carcinogenesis and Chemoprevention Program of the Masonic Cancer Center, University of Minnesota, a National Cancer Institute designated Comprehensive Cancer Center. I currently lead a research group of 10-15 scientists with B.S., M.S., or Ph.D. degrees in the chemical and biological sciences. Our research, which focuses on mechanisms and prevention of cancer induced by tobacco products and environmental agents, is fully funded by grants from the U.S. National Cancer Institute and the National Institute of Environmental Health Sciences. I am the principal investigator of three R01 grants and a program project (P01) grant, from the National Cancer Institute and co-investigator on a number of other grant and cooperative agreement awards from the National Institutes of Health and the Food

and Drug Administration. I have been awarded a Merit Award (10 years of funding) and an Outstanding Investigator Grant (14 years of funding) from the National Cancer Institute. My research has been recognized by a number of prestigious awards, including election as a Fellow of the American Association for the Advancement of Science, a Fellow of the American Chemical Society, and a Research Professor of the American Cancer Society. To the best of my knowledge, I am the only scientist who has ever held the latter two awards from the American Chemical Society and the American Cancer Society simultaneously. I received the American Association for Cancer Research/Cancer Research and Prevention Foundation Award for Excellence in Cancer Prevention Research in 2006 and the Founders Award from the Division of Chemical Toxicology, American Chemical Society, in 2009. I received the Joseph Cullen Award from the American Society of Preventive Oncology in 2012. I received the William Cahan Distinguished Professor Award from the Flight Attendant Medical Research Institute in 2002 and the Alton Ochsner Award Relating Smoking and Health in 2001. I received the Minnesota Award from the Minnesota Section of the American Chemical Society in 2017. I am a member of the Academy for Excellence in Health Research and the Academy for Excellence in Team Science at the University of Minnesota. My publication entitled "Tobacco Smoke Carcinogens and Lung Cancer", published in the Journal of the National Cancer Institute in 1999, can be found on the University of Minnesota Medical School "Wall of Scholarship" because it was cited more than 1,000 times in the peer-reviewed literature. I served as Editor-in-Chief of the American Chemical Society journal *Chemical Research in Toxicology* from 2013-2017 and as an Associate Editor of the *Journal of Medicinal Chemistry* from 2004-2012.

Respected researchers are invited by the National Institutes of Health as well as private foundations to serve on peer review groups for evaluation of research proposals submitted by scientists from the U.S. and abroad. I was chair of the "Chemo-Dietary Prevention Study Section" of the NIH from 2006-2009, and served on the "Chemical Pathology Study Section" from 1981-1985. I was on the Board of Scientific Counselors of the National Cancer Institute from 2001-2004. I served on the "Carcinogenesis, Nutrition, and the Environment Study Section" of the American Cancer Society from 1998-2001, and as its Chair in 2001. I served on the American Cancer Society "Council for Extramural Grants" from 2010-2014. I served on the "Grants Review Panel" for the American Institute for Cancer Research from 1984-1987. I currently serve, since 2011, on the National Cancer Institute "PREVENT Study Section." I continue to be in demand as an ad hoc member of multiple other peer review panels.

Numerous other service activities to the scientific research community are listed in my Curriculum Vitae. I note some of the more important ones here. I have served on multiple writing groups for the International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans. This important and prestigious series reviews and evaluates specific exposures and chemicals for evidence of carcinogenicity. Each committee member reviews a significant aspect of the literature and prepares a lengthy and detailed written

document. These documents are reviewed and discussed in a 10 day meeting in Lyon, France resulting in an evaluation of carcinogenic activity to humans and ultimately the publication of a monograph. The series is currently in Volume 127. I served on the Monograph Committees on "Tobacco Habits Other than Smoking," Volume 37, 1985; "Tobacco Smoke and Involuntary Smoking", Volume 83, 2002; "Betel Quid and Areca Nut," Volume 85, 2003, as committee Chair; "Smokeless Tobacco and Some Related Nitrosamines," Volume 89, 2004, and "A Review of Human Carcinogens; Lifestyle Factors," Volume 100E, 2009. I was a member of the National Toxicology Program Board of Scientific Counselors from 1997-2001 and the Science Advisory Board for the National Center for Toxicological Research from 1998-2002. I was on the Board of Scientific Counselors for the Division of Cancer Etiology of the National Cancer Institute from 1989-1995. I was Chair of the Division of Chemical Toxicology of the American Chemical Society from 1999-2000. I served on the Health Research Committee of the Health Effects Institute from 1992-1996. I have also served on numerous advisory groups for academic research centers specializing in toxicology and cancer research.

I am in demand as a speaker on topics pertinent to cancer prevention research, with particular emphasis on tobacco and cancer including basic, applied, and epidemiologic studies on nitrosamines. I have given formal invited lectures worldwide averaging about five per year since 2002 in almost every state of the U.S. and at scientific conferences and universities in Europe, Asia, and South America.

I have published over 880 original manuscripts, book chapters, reviews, and other peer reviewed documents in the scientific literature. This includes more than 600 original research articles in peer-reviewed journals. More than half of these original research articles are concerned with nitrosamines, including nitrosodimethylamine (NDMA), also known as dimethylnitrosamine (DMN). My H-index is 91, and my articles have been cited more than 35,000 times.

My first publication on nitrosamines was in 1974 when my colleagues and I discovered *N'*-nitrosonornicotine (NNN) in smokeless tobacco. This was the first example of a carcinogenic nitrosamine in unburned tobacco; in fact, the first example of any carcinogen in unburned tobacco. This paper was published in *Science*, and revolutionized the characterization and carcinogenicity assessment of tobacco products.

In the 1970s when my research on nitrosamines began, there was great interest in these compounds as potential carcinogenic constituents of food, drugs, tobacco products, and other consumer products. In 1956, Magee and Barnes had published their groundbreaking study demonstrating that NDMA caused liver cancer in rats. This was remarkable because NDMA is a water-soluble compound with only 11 atoms, and it had been supposed at the time, based on studies of polycyclic aromatic hydrocarbons, that carcinogenic agents were typically larger fat soluble compounds. The Magee and Barnes study stimulated an explosion of research on nitrosamines including extensive carcinogenicity testing and analysis

projects. Beginning in the 1970s, the U.S. Food and Drug Administration held regular meetings to address critical issues such as the contamination of bacon with *N*-nitrosopyrrolidine and related volatile nitrosamines including NDMA. Numerous analytical methods were developed for volatile nitrosamines such as NDMA in particular. The challenge was to be able to quantify relatively low levels of nitrosamine contaminants in common food and drug products. This was before the development and common use of highly sensitive mass spectrometers which are the current instruments of choice for the routine analysis of nitrosamines. Various methods were developed, but the one that was ultimately widely used was "Thermal Energy Analysis," in which the nitrosamine molecule was split and the released NO detected. This method was developed by a small company - Thermo Electron Corporation - now the huge instrument and scientific products corporation Thermo Fisher Scientific. The Thermal Energy Analyzer method was applied to numerous products and NDMA contamination was found in products such as beer, cured meats, and others. There was sufficient interest in nitrosamines in the period 1973-1996 that the International Agency for Research on Cancer sponsored biennial meetings for presentation of research on nitrosamines. These meetings were typically attended by 200-300 participants. Ultimately, the levels of common volatile nitrosamines such as DMN in most consumer products were decreased by process modifications and their concentrations rarely exceeded 5-10 ppb (0.005-0.01 ppm).

Our research on carcinogens in tobacco products fit very well into this framework of international interest, and we pursued it aggressively. Using my skills in analytical organic chemistry and mass spectrometry, and working together with an outstanding interdisciplinary team at the American Health Foundation, we carried out studies on the analysis of nitrosamines in tobacco products, the formation and synthesis of tobacco-specific nitrosamines, and the carcinogenicity of nitrosamines including tobacco-specific nitrosamines, cyclic nitrosamines, and other nitrosamines found in consumer products. We then extended our studies to investigate the metabolism of nitrosamines in laboratory animals and humans, and based on these studies developed biomarkers of nitrosamine exposure by quantifying nitrosamine metabolites in human urine. This research led to further investigations of human exposure to nitrosamines, particularly tobacco-specific nitrosamines. In a series of studies with significant policy implications, we demonstrated consistent exposure of non-smokers to carcinogenic tobacco-specific nitrosamines such as NNK via secondhand tobacco smoke in the home and a variety of commercial settings. These studies analyzed urinary NNAL, a metabolite of the lung carcinogen NNK, and contributed significantly to research supporting the clean air acts that have virtually eliminated indoor smoking, a known cause of lung cancer in non-smokers. Our studies on nitrosamine metabolism led logically to research on the interaction of their metabolites with DNA, the critical step in cancer induction by nitrosamines and other carcinogens. Our group characterized most of the DNA adducts formed by tobacco-specific nitrosamines and related cyclic nitrosamines. This research took advantage of my strong background in organic chemistry and analytical chemistry, particularly with the application of mass spectrometry.

Thus, as a result of more than 45 years of research in chemical and tobacco carcinogenesis, much of it focused on nitrosamines, I am thoroughly familiar with the state of the art in the formation, quantitative analysis, chemistry, biochemistry, metabolism, carcinogenicity, human exposure biomarkers, and DNA damage by nitrosamines. I currently serve on the European Food Safety Authority panel evaluating nitrosamines in food. I also served on the expert panel for the FDA Workshop entitled "Nitrosamines as Impurities in Drugs: Health Risk Assessment and Mitigation Public Workshop," March 29, 2021.

II. Nitrosamines

1. Chemical structures.

Nitrosamines are simple organic compounds formed by the attachment of an N=O group to an amino nitrogen.

2. Formation of nitrosamines

The formation of nitrosamines from secondary amines is textbook organic chemistry, a reaction familiar to all students in their first encounter with organic chemical reactions.[1,2] The nitrosation of secondary amines occurs so easily that it was once widely used in qualitative organic analysis as a test for the presence of a secondary amine, but after the discovery of nitrosamine carcinogenesis, this was eventually discontinued. Secondary amines such as dimethylamine and diethylamine are easily nitrosated by the agent nitrous anhydride (N_2O_3), which is formed from 2 molecules of nitrous acid (HNO_2), the conjugate acid of sodium nitrite ($NaNO_2$).[3] N_2O_3 reacts rapidly with a secondary amine such as dimethylamine or diethylamine to form the corresponding nitrosamine, in this case NDMA or *N*-nitrosodiethylamine (NDEA), respectively. The optimal pH for this sequence of reactions is 3.4, but it occurs over a wide range of pH values including at a pH 7 (neutral) with varying rates as expressed by the equation:

Rate = k [amine][nitrite]^2.

Tertiary amines can also be nitrosated to form dialkylnitrosamines such as NDMA.[4] Nitrosation of nicotine to produce NNK and NNN is a well-known example of tertiary amine nitrosation.[5] Nitrosation reactions can occur at neutral and basic pH with catalysis by formaldehyde[6] and can be inhibited by ascorbic acid.[7] Regarding the formation of NNK and NNN, we applied the known nitrosation chemistry to demonstrate that nicotine could be converted to 3 nitrosamines - NNK, NNN, and NNA.

This groundbreaking research established the chemical basis of nicotine nitrosation that eventually led to the identification of NNK in tobacco and tobacco smoke.[8,9] The identification of NNK in tobacco products then led to its testing for

carcinogenicity, which showed that it is a potent lung carcinogen in multiple animal species, independent of the route of administration, inducing mainly adenocarcinoma of the lung, now the major type of tumor seen in cigarette smokers.[10]

3. Analysis of nitrosamines

A great deal of effort has been devoted to the analysis of nitrosamines in various settings including food, drinking water, tobacco products, beer, medicines, and other consumer products. The rationale for these detailed and extensive studies derives from the powerful carcinogenicity of these compounds, for which the scientific community has consistently raised concerns about human exposure. Highly reliable analytical methods for determination of trace amounts of nitrosamines have existed for decades – first the nitrosamine specific "Thermal Energy Analysis" noted above and in more recent years sophisticated and sensitive mass spectrometric methods. All of these methods have been extensively validated for accuracy, precision, sensitivity, and overall reliability, and all existed prior to and during the development of the manufacturing processes at issue. The earlier analyses of preformed nitrosamines in food and beverages have been reviewed. In a representative summary, levels of "volatile nitrosamines" such as NDMA and NDEA in at least 60 different food types were recapitulated, typically being found in the 0-10 parts per billion range (micrograms per kilogram, or micrograms per liter), with occasional exceptions often involving foods preserved by smoking or related techniques. Levels of volatile nitrosamines in food are now generally lower in part because of regulations regarding the amount of nitrite that can be used.[11] A recent review has summarized current analytical data on human exposure to preformed nitrosamines.[12,] Nitrosamine levels in tobacco, food and beverages, drinking water, and personal care products were presented. The highest average levels were found in tobacco products (16,100 ng/g), followed by personal care products (1500 ng/g), while the lowest amounts were found in food and beverages (6.7 ng/g). Maximum average exposure to nitrosamines was estimated at about 25 μg per day, driven mainly by use of tobacco products.

4. Carcinogenicity of nitrosamines and NDMA in particular

In a landmark publication, Magee and Barnes first demonstrated the carcinogenicity of NDMA.[13] The substance was administered in the diet of rats (10 male and 10 female) at a concentration of 50 ppm. Between the 26th and 40th week, 19 of the treated animals developed primary hepatic tumors, with metastases in 7 cases. This remarkable finding initiated an entire branch of research ultimately resulting in the discovery of nitrosamines that readily and specifically induced tumors in virtually all major organs. High doses of NDMA are lethal; a median lethal dose in rodents of 20-40 mg/kg body weight has been reported.[14] The principal mechanism of death is severe hemorrhagic necrosis of the liver.[15] Consistent with this, cases of human poisoning by NDMA have been reported when large amounts of

the compound were used without precautions or when NDMA was used in deliberate attempted murders.[16]

The carcinogenicity of NDMA was demonstrated in several different strains of rats. Long-term administration of non-lethal doses of NDMA, typically about 4 mg/kg bw/day, consistently produced high incidences of hepatocellular carcinomas and cholangiocellular tumors. Short term administration of high doses of NDMA typically produced kidney tumors in multiple studies. The carcinogenicity of NDMA was significantly reduced by substitution of its methyl hydrogens with deuterium; the resulting deuterium isotope effect retarded its metabolic activation.[17] An extensive dose-response study of NDMA and NDEA on 4,080 rats demonstrated that a dose of 1 ppm of NDMA or NDEA in the drinking water caused about 25% of the rats to develop a liver neoplasm, a dose of 0.1 ppm caused about 2.5% to do so, and a dose of 0.01 ppm caused about 0.25% to do so, etc., with no indication of a "threshold."[18] In a study carried out by our group, the carcinogenic activities of NDMA and the tobacco-specific lung carcinogen NNK were compared.[19] Groups of 30 male F-344 rats were given 60 s.c. injections of 0.0055 mmol/kg of either NNK or NDMA over a 20 week period (total dose, 0.33 mmol/kg) and the experiment was terminated after 104 weeks. NDMA induced liver tumors in 6 of 30 rats; NNK induced a similar number of liver tumors but also a high incidence of lung adenocarcinoma and nasal cavity tumors.

The carcinogenicity of NDMA has been demonstrated in multiple species.[20] In Syrian golden hamsters, it induced various types of liver tumors when given by gavage or in the drinking water. Chinese hamsters and European hamsters also developed liver tumors when administered NDMA by injection. Guinea pigs developed liver tumors when given NDMA in the diet. Rabbits given NDMA in the diet developed liver carcinomas with lung metastases. Rainbow trout given NDMA in the diet developed hepatocellular tumors. Various strains of mice injected with NDMA developed liver and lung tumors. Liver tumors were also observed in mastomys administered NDMA by subcutaneous injection. Guppies and frogs exposed to NDMA in aquarium water resulted in the development of liver tumors. Rabbit, mink, blue fox, and duck are additional species in which NDMA induced liver tumors.

The pharmacokinetics and DNA binding of NDMA have been studied in detail in a range of species including mice, rats, rabbits, hamsters, dogs, pigs, and monkeys. Consistently, these studies have demonstrated high systemic clearance and high oral bioavailability of NDMA. In one study, NDMA was rapidly excreted into the saliva after i.v. and p.o. administration to dogs.[21] A consistent and linear pharmacokinetic and metabolic pattern emerged in these studies resulting in the conclusion that extrapolation to humans of conclusions obtained in studies using laboratory animals was justified.[22,23,24,25]

Similarly, the carcinogenicity of NDEA, which is more potent than NDMA, has been demonstrated in multiple species including in various different strains of rat,

mouse, and hamster as well as guinea pigs, chickens, rabbits, cats, dogs, pigs, monkeys, gerbils, snakes, hedgehogs, grass frogs, birds, and fish.[26] Dr. Lance Molnar, Ph.D., Mylan's Senior Director, Global Pharmacology and Toxicology, testified in his deposition that both NDMA and NDEA "are genotoxic carcinogens … in every experimental animal that they've been evaluated in" and are "demonstrated to produce tumors."[27]

In summary, NDMA and NDEA have been extensively tested in multiple species and at extremely low doses. Very few, if any, other chemicals have been so thoroughly tested for carcinogenicity, producing uniformly positive results. These data leave no doubt as to the high potency of NDMA and NDEA to induce tumors in laboratory animals and likely in humans. The lethality of NDMA at high doses has been observed in both laboratory animals and humans.

It is worth noting that both NDMA and a structurally related compound, dimethyl sulfate, are classified by IARC as belonging to Group 2A, "probably carcinogenic to humans."[28,29] According to the IARC Monographs preamble, this category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. Of importance, IARC classification does not consider or indicate the strength of carcinogenicity. Thus, while NDMA is a far more potent carcinogen than dimethyl sulfate, both are classified as Group 2A. In an interesting exchange between Min Li of ZHP and ZHP's consulting toxicologist, Charles Wang, Ph.D., Dr. Wang advised that NDMA should actually be classified as Class 1B, stating: "Looks like IARC does consider NDMA as a Class 2A agent. However, according to the definition of Class 2 in ICH M7(R1) guideline, the Class 2 compound should be a 'Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)'. There are plenty rodent carcinogenicity data for NDMA (see revised report in the attached, page 4). In Fisher MSDS, NDMA has been classified as Class 1B for carcinogenicity (attached)."[30] In addition, NDMA is not classified in Group 1, "carcinogenic to humans", as there is no instance, other than the poisoning murder incidents noted above, in which humans have been exposed exclusively to relatively low doses of NDMA in the absence of other potentially carcinogenic exposures; exposure to nitrosamines always occurs in mixtures. The exception to this IARC classification is the tobacco-specific nitrosamines NNK and NNN, to which human exposure also occurs as mixtures with other tobacco constituents (their carcinogenic activities and concentrations in tobacco products, particularly smokeless tobacco, along with sufficient metabolic data, lead to the higher classification).[31] Carcinogenicity data for dimethyl sulfate were summarized in the IARC Monographs.[32] Of course, as recognized below, it would be unethical to perform studies on the effects of NDMA and NDEA on humans due to their potency, consistent with the routine use of nitrosamines to cause cancer in laboratory animals.

More than 200 nitrosamines of different chemical structures (e.g., different R groups attached to the N-N=O group) have been tested for carcinogenicity and at

least 199 of them cause tumors in laboratory animals.[33] Nitrosamines are frequently organospecific in these studies, meaning that, depending on the structure of the nitrosamine, specific organs or tissues may be affected. Thus, for NDMA, the main target tissues demonstrated in animal studies are the liver and kidney, independent of the route of administration and species in which the test is performed. NDEA also targets these tissues in addition to causing tumors of the esophagus. In contrast, di-*n*-butylnitrosamine causes mainly tumors of the urinary bladder in several different animal species, while methylbenzyl nitrosamine specifically causes esophageal tumors in rats. These organospecific characteristics of nitrosamine carcinogenesis have been linked to their metabolism in specific tissues. Metabolism is absolutely required for the carcinogenicity of nitrosamines and it has been established that α-hydroxylation (replacement of the hydrogen atom adjacent to the N-N=O group by a hydroxyl group) catalyzed by specific cytochrome P450 enzymes present in the liver and other tissues, is the major pathway of metabolism leading to carcinogenesis. Multiple human tissues contain these enzymes and can metabolize nitrosamines; therefore, it is likely that when exposed to nitrosamines, humans are susceptible to developing a wider spectrum of cancers targeting additional organs. There are some instances of concordance between target tissues of nitrosamine carcinogenesis in laboratory animals and in humans. One example is the tobacco-specific nitrosamine NNN, mentioned above. NNN causes esophageal and oral tumors in rats. A prospective epidemiology study carried out in male cigarette smokers in Shanghai demonstrated a strong relationship between NNN exposure (as determined by NNN in urine) and esophageal cancer in the study subjects. NNN is also the only strong oral carcinogen in smokeless tobacco, a known cause of oral cancer in humans.

5. Carcinogenicity of nitrosamines in humans

Exposure to nitrosamines, including NDMA and NDEA, is a likely cause of cancer in humans. For example, there are examples of human poisoning by NDMA which coincide with toxicity studies in rats, as noted above. Human metabolism of NDMA, NDEA, and other nitrosamines by the pathways known to lead to DNA damage - identical to that seen in rats that developed tumors upon treatment with these nitrosamines - has been demonstrated in numerous studies using various experimental systems. These included human liver slices, human liver subcellular fractions such as microsomes (with activity just as high as rat liver microsomes), and explant cultures of various human tissues including bronchus, esophagus, bladder, and colon.[34] These results are consistent with the known activities of human hepatic cytochrome P450 enzymes such as P450s 2E1 and 2A6, which efficiently metabolize NDMA and NDEA.[35] DNA adducts known to result from NDMA and NDEA such as 7-methylguanine and O^6-methylguanine have been detected in human tissues.[36,37,38]

Thus, pathways of metabolism and DNA damage observed in humans clearly replicate those in laboratory animals that developed tumors upon treatment with NDMA. There is no reason to doubt that humans are susceptible to carcinogenesis

by NDMA and NDEA, considering their powerful carcinogenicity and the immense amount of supporting biochemical and toxicological data which are available. For example, among all nitrosamines, the tobacco-specific nitrosamines NNN and NNK are widely recognized as human carcinogens because of the high levels of human exposure.[39,40,41] In a study of exposures to British workers in the rubber industry, it was concluded that, "Consistent with previous studies, *N*-nitrosamines exposures in the rubber industry, were associated with mortality from cancers of the bladder, lung, stomach, leukaemia, multiple myeloma, oesophasus, prostate, pancreas and liver."[42]

Collectively, these observations support the human carcinogenicity of nitrosamines in general, which are potent mutagenic carcinogens. There is no reason to expect that humans would differ from laboratory animals with respect to the existence of nitrosamine carcinogenesis. All of the main metabolic activation pathways of nitrosamines that occur in laboratory animals treated with these compounds also occur in human tissues. The DNA adducts that are formed are identical. For example, treatment of laboratory animals with NDMA causes the formation of 7-methylguanine and O^6-methylguanine in DNA; the latter is known to cause mutations, specifically G to A mutations.[43] The exact same DNA adducts and mutations are found in human tissues exposed to NDMA in vitro. Given sufficient exposure to NDMA and NDEA, as with the levels found in the contaminated valsartan (see below), the formation of these DNA adducts would be sufficient to cause mutations and cancer in exposed humans.

The World Health Organization published a peer reviewed analysis of the carcinogenicity of NDMA in 2002.[44] The findings include: "Based upon laboratory studies in which tumours have been induced in all species examined at relatively low doses, NDMA is clearly carcinogenic and clastogenic. …. Qualitatively, the metabolism of NDMA appears to be similar in humans and animals; as a result, it is considered highly likely that NDMA is carcinogenic to humans, potentially at relatively low levels of exposure."[45] In the Effects Evaluation, with regard to Carcinogenicity, the study states: "The weight of evidence of the carcinogenicity of NDMA in mammalian species is consistent and convincing. Moreover, the pattern of tumour development is characteristic of that for a mode of action of carcinogenesis involving direct interaction with genetic material. In available studies, NDMA has induced tumours in all species examined (mice, rats, hamsters), at relatively low doses in some cases, irrespective of the route of exposure (oral, inhalation); tumours were induced in a wide range of tissues, including the liver, Leydig cells, lungs, kidney, and nasal cavity, in the absence of significant non-neoplastic effects, in the limited number of studies in which these were well examined. …. NDMA has been consistently mutagenic and clastogenic in human and rodent cells exposed *in vitro*. …. DNA adducts (in particular, O6-methylguanine) formed by the methyldiazonium ion generated during metabolism likely play a critical role in NDMA carcinogenicity. …. Putative pathways for the metabolism of NDMA are similar in rodents and humans, and indeed the formation of O6-methylguanine has been detected in human tissues exposed to NDMA. Therefore, owing to the

considerable evidence of carcinogenicity of NDMA in laboratory species, evidence of direct interaction with DNA consistent with tumour formation, and the apparent lack of qualitative species-specific differences in the metabolism of this substance, NDMA is highly likely to be carcinogenic to humans."[46]

ZHP cited to the WHO article in its Deviation Investigation Reports, and Min Li, Ph.D., Vice-President for Analytical Operations for ZHP, confirmed that this was because the article was considered to be scientifically reliable.[47] Dr. Li, who holds a Ph.D. in Organic Chemistry from Johns Hopkins University, also confirmed that ZHP stated in its own Deviation Investigation Report that NDMA is, "a probable, you know, carcinogenic to human."[48] ZHP also stated in the Deviation Investigation Report for the TEA process that "NDEA is considered as a probably human carcinogen based on projection from the animal studies." ZHP cited to Pharmol. Ther., 1996, Vol. 71, Nos. 1/2, pp. 57-81 for this. ZHP also cited to Int. J. Biol. Sci. 2013, Vol. 9, No. 3, pp.237-245 for the observation that NDEA "is one of the most potent chemical hepatocarcinogens of this class, which can induce a variety of liver lesions in rodents."[49] Min Li also confirmed that there are no studies deliberately performed on humans with regard to the carcinogenicity of nitrosamines because it would be unethical to knowingly give NDMA to humans, as a result of the risk of cancer. More to the point, Min Li confirmed that it would be unethical "to give humans NDMA in the levels that were found in the valsartan pills."[50]

Min Li also testified with regard to information provided to ZHP by ZHP's consulting toxicologist, Charles Wang, Ph.D. Dr. Wang advised ZHP regarding the risk associated with the NDMA and NDEA in the valsartan, and his analysis was the basis for the toxicological assessment found in the Deviation Investigation Reports.[51] Min Li confirmed that Dr. Wang was consulted because he was deemed an expert who would be trusted to provide "reliable information."[52] Among other things, Dr. Wang advised ZHP that the classification of NDMA as a Class 2A agent was incorrect, and should instead be designated as Class 1B, since, "There are plenty rodent carcinogenicity data for NDMA."[53] In addition, Dr. Wang consulted what he termed, "a carcinogenicity expert consultant to perform the analysis who knows risk assessment of carcinogen and kept updated in regulatory guideline and standards in this field." In an email dated July 6, 2018, this expert, James McDonald, Ph.D., advised Dr. Wang – who relayed this information to Min Li - that, "the body of evidence on this suggests pretty clearly that this is a likely human carcinogen at sufficient exposures. The argument that the company would have to make to keep this product on the market will be very difficult with this profile. I'm not exactly sure where one would begin given the very high levels [his understanding was 30 ppm per a prior email from Dr. Wang] you think they are seeing. …. I expect this is not what they would want to hear but, unless there is a compelling reason to leave this product on the market (e.g.: only product available to treat a serious, life-threatening disease), I would expect the FDA would ask for a recall."[54]

Bandaru Venkata Ramarao, Vice President of Quality Control for Hetero Unit 5 (the finished dose manufacturing division of Hetero) also testified to the

significant carcinogenic risk presented by the NDMA contamination of Hetero's valsartan. In discussing the FMEA (Failure Modes and Effects Analysis) risk evaluation performed by Hetero, Mr. Ramarao testified that the severity of the hazard presented by the NDMA impurity, "was at the highest level because of the level of NDMA and because it's a probable carcinogen. . ." The Health Hazard was described in the FMEA as "Identified impurity is carcinogenic in nature," and he agreed this meant, "this is something that can cause cancer. . ." Finally, he confirmed that the overall risk priority number, or RPN, was the maximum possible score of 125, meaning it was deemed, "intolerable."[55] Mr. Ramarao was also asked about the 2002 WHO publication discussed above, and agreed that, "Because of these health effects that we are talking about and the risk of cancer, it would never be acceptable to knowingly sell valsartan containing NDMA... ....[T]hat's the reason why the valsartan that was sold by Unit 5 with the levels of NDMA that were seen, that never would have knowingly been done if you had known the NDMA was there because of that health risk."[56] Mr. Ramarao agreed that due to the GMP failures that resulted in the NDMA contamination, "the result of that was that NDMA ended up in the valsartan, which is something that causes cancer," and the risk, "was assessed at the highest level because people ingesting NDMA at the levels that were found in these pills is something that will increase their risk for cancer...."[57]

The likely carcinogenicity of NDMA (and NDEA) in humans is also demonstrated by regulatory guidelines. For example, the 2013 ICH M7 Draft Consensus Guideline, and 2015 ICH M7 Guidance for Industry, titled Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, include *N*-nitroso compounds in the "cohort of concern" of "high potency mutagenic carcinogens" that are excepted from the acceptable intake levels set forth for DNA reactive substances.[58] The same is found in the December 2008 FDA Draft Guidance for Industry titled Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches: "However, there are some compounds containing certain structural groups (aflatoxin-like-, *N*-nitroso-, and azoxy-structures) that have extremely high carcinogenic potency and are excluded from the threshold approach."[59] The EMA takes the same approach. In discussing a group of "high potency genotoxic carcinogens" including nitrosamines, the "Guidelines on the Limits of Genotoxic Impurities" in effect from January 2007 to January 2018, states in part: "Some structural groups were identified to be of such high potency that intakes even below the TTC would be associated with a high probability of a significant carcinogenic risk."[60]

Lance Molnar, Ph.D., Mylan's Senior Director, Global Pharmacology and Toxicology,, agreed in his deposition that nitrosamines are treated as non-threshold by "the EMA, FDA, ICH … regulatory bodies in general" and that "non-threshold effect would mean that a single molecule could be detrimental."[61] Accordingly, Mylan's Toxicology report stated that "[t]his potential for carcinogenic activity is considered the critical effect of these compounds (*N*-nitrosamines) as it can theoretically occur at doses far lower than those required to produce alternative

toxicities after either acute or repeated exposures."[62] Similarly, Mylan's Medical Risk Assessment stated the following: "the potential risk associated with potential exposure to NDEA above the defined specification is significant and [risk of harm to patients] cannot be excluded."[63]

Studies published in the dietary literature are of course quite significant to this analysis. One study concluded, "our results suggested that there was a positive association between NDMA intake and gastrointestinal cancer risk, specifically of rectal cancer."[64] Another study recognized "challenges to nutritional epidemiological research on the relationship between dietary nitrosamines and cancer occurrence," but found "an increased risk of colorectal cancer among individuals with a high intake of NDMA."[65] The authors of yet another study concluded in part, "According to our study, processed meat intake was positively associated with cancers of the oesophagus, stomach, colon, rectum, larynx, lung, breast, prostate, and urinary bladder. Therefore, processed meat could be said to act as a multi-organ carcinogen among humans." The authors pointed to nitrosamines as a potential causative agent.[66]

This body of literature also includes studies cited and analyzed in the 2002 WHO article discussed above, which includes Risch, H.A., Jain, M., Choi, N.W., Fodor, J.G., Pfeiffer, C.J., Howe, G.R., Harrison, L.W., Craib, K.J., and Miller, A.B. (1985) Dietary factors and the incidence of cancer of the stomach, *Am J Epidemiol. 122*, 947-59; González, C.A., Riboli, E., Badosa J., Batiste, E., Cardona, T., Pita, S., Sanz, J.M., Torrent, M., and Agudo A. (1994) *Nutritional factors and gastric cancer in Spain, Am J Epidemiol. 139*, 466-73; La Vecchia, C., D'Avanzo, B., Airoldi, L., Braga, C., and Decarli, A. (1995) Nitrosamine intake and gastric cancer risk, *Eur. J. Cancer Prev. 4*, 469-74; Pobel, D., Riboli, E., Cornée J., Hémon, B., and Guyader, M. (1995) Nitrosamine, nitrate and nitrite in relation to gastric cancer: a case-control study in Marseille, France, *Eur J Epidemiol. 11*, 67-73; Rogers, M.A., Vaughan, T.L., Davis, S., Thomas, D.B. (1995) Consumption of nitrate, nitrite, and nitrosodimethylamine and the risk of upper aerodigestive tract cancer, *Cancer Epidemiol Biomarkers Prev. 4*, 29-36; Goodman, M.T., Hankin, J.H., Wilkens, L.R., and Kolonel, L.N. (1992) High-fat foods and the risk of lung cancer, *Epidemiology 3*, 288-99; De Stefani, E., Deneo-Pellegrini, H., Carzoglio, J.C., Ronco, A., Mendilaharsu, M. (1996) Dietary nitrosodimethylamine and the risk of lung cancer: a case-control study from Uruguay, *Cancer Epidemiol Biomarkers Prev. 5*, 679-82. In La Vecchia, et al., 1995, at 471, the authors concluded, "This study found a moderate but significant association between exogenous NDMA intake and gastric cancer risk. The association was consistently observed across strata of sex and age." In Gonzalez, et al., 1994, at 469, the authors commented on the association with gastric cancer, stating that they, "observed an increased risk associated with an elevated consumption of exogenous nitrosamines in both intestinal and diffuse types." In De Stefani, et al., 1996, at 681, the authors concluded, "In summary, NDMA intake was associated in this particular population with an increased risk of lung cancer." In Pobel, et al., 1995, at 70-71, the authors found: "In the present study we assess the risk of gastric cancer in relation to estimated dietary intake of nitrate, nitrite, and NDMA. The most important feature

revealed by this investigation is the increased risk associated with increasing intake of exogenous NDMA." In recognizing the complexity of the analysis, the authors concluded, "However, the findings presented here are consistent with the biological hypothesis and provide support for an association between nitrosamines and gastric cancer." In Goodman, et al., 1992, at 296, the authors concluded in part, "*N*-Nitroso compounds have been shown to be mutagens and important carcinogens for a number of target organs, such as the liver, stomach, brain, and lung. In this analysis, we found a strong relation between consumption of nitrite in men, and dimethylnitrosamines in men and women, and the risk of lung cancer." In Rogers, et al., 1995, at 33, the authors concluded in part that, "consumption of foods high in NDMA resulted in an elevated risk of cancer," in the "upper aero-digestive tract." In Risch et al., 1985, at 956, the authors concluded: "In summary, our data strongly suggest, in consonance with several previous studies, that nitrite intake is associated with risk of stomach cancer occurrence. Whether this relationship is mediated through the conversion of nitrite to *N*-nitroso compounds is unclear, although some protection appears to be afforded by consumption of citrus fruit."

To the extent these or other studies do not find a significant association, or raise questions, this can be explained by small or relatively small sample size, inadequate follow up period to capture all cancers, bias/inadequate dose quantification, potentially mitigating dietary factors such as vitamin C intake, and others.

Anticipating potential responses regarding proof of a cause and effect relationship, aside from the fact that a study cannot be ethically constructed to deliberately administer NDMA or NDEA to humans, this has been addressed. For example, in one article published in 1984 the authors noted the impediments to definitively proving cause and effect, "due to the insensitivity of the epidemiological instruments available today and to the lack of truly unexposed populations that could be used as controls." The authors stated in part, "Although a causal association between nitrosamine exposure and human cancer has not yet been rigorously established, the recognized association between exposure to nitrosamines in unburned tobacco products such as smokeless tobacco and oral cancer in humans is as close as one is likely to get in epidemiological studies of this class of carcinogens. In addition, biochemical, pathological, and experimental data provide little evidence that humans are resistant to the carcinogenic action of NOC [*N*-Nitroso compounds], from either preformed or endogenous sources… Although quantitative differences exist between rodents and humans in repair of DNA alkylation damage, the mechanisms of repair of this damage appear to be the same. Recently, malignant transformation of human pancreatic epithelial cells by NDMA has been reported."[67] A meta-analysis that noted varied results in studies that were reviewed, and the strengths and limitations of the study at hand, primarily based on difficulties in studying the effects of food intake, concluded in part that the risk of gastric cancer could be increased by "high consumption" of NDMA. The authors specifically noted: "When daily NDMA intake reached 0.12 ug, the harmful effect to human became more obvious."[68] For perspective, 0.12 ug (micrograms) is

equivalent to 120 ng (nanograms), and in a 320 mg dose of valsartan would equate to 0.375 ppm. These levels are in line with the levels established by the FDA, and were exceeded by the vast majority of the valsartan tested for nitrosamine contamination.

The EMA evaluated the valsartan contamination and concluded that the levels of NDMA and NDEA should be reduced to the maximum extent possible, but set thresholds consistent with the FDA's thresholds, factoring in the potential for nitrosamines to exist due to background levels for example in water. The statement firmly recognizes that there is no technically safe level, and the establishment of the thresholds is the product of a risk benefit analysis. Even though the EMA concluded that the risk is relatively low, that is also a finding of a real risk that is unacceptably dangerous, hence the establishment of the threshold levels.[69] Of interest as well, the EMA statement cites to and discusses a study performed in Denmark regarding the risk posed by the valsartan contamination, and found an increased risk for colorectal cancer and uterine cancer.[70] The EMA commented that the 4.6 year follow up interval was likely too short, and that the number of people studied too small, to draw any firm conclusions based on the data.[71]

A recently published study utilized data from a German health insurance database.[72] The cohort included those who filled at least one prescription of potentially contaminated valsartan from 2012 to 2017. The article refers to the establishment of whether or not the valsartan was manufactured utilizing API from ZHP, but without analysis of which manufacturing process was used. Thus, there is a concerning lack of data as to the extent to which those consuming potentially contaminated valsartan actually consumed contaminated valsartan. The endpoint was a cancer diagnosis. A statistically significant association for liver cancer was identified, but no association was identified for the overall risk of cancer or for other specific cancers. The authors pointed out that "molecular mechanisms known for NDMA in the pathogenesis of liver cancer in experimental animals support an association with NDMA exposure in humans. It may be that NDMA exposure promotes cancer development in already existing, as yet undiagnosed early stages and thus hastens clinical manifestation." They also recognized that, "The immediate recall of all potentially NDMA-contaminated valsartan drug products by regulatory authorities world wide was necessary in order to protect the public health." Thus, even with the limitations set forth in the study and discussed below, the study supports the conclusion that the contaminated valsartan increases the risk of cancer.

The study actually contrasts itself with Pottegard, discussed above in the context of the EMA statement, and points out the small number of people (5,150) evaluated in that study, and the small number of cancers in that study, and thus an inadequate sample size, by contrast to the large number of people studied in this study (780,871), which is a strength of the study. However, the study does recognize some significant limitations, including lack of information regarding the

NDMA content of the valsartan taken by those studied, and the short three year follow up.

Min Li, Ph.D. of ZHP testified with regard to a recent study published by Yoon et al. from South Korea.[73] Dr. Li testified suggested that this study supported the notion that NDMA would not increase the risk of cancer in a human.[74] The study addresses multiple limitations on its face and also suffers from a significant flaw that led the authors to retract the article. Yoon relied on a 2016 study by Zeng which found that "NDMA excreted in urine after ranitidine intake was 95.6 ng/mL, which was a 430-fold increase than before ranitidine use."[75] Yoon relied on those figures, and further added that "[a]ctual systemic NDMA exposure is likely much higher than that eliminated in urine."

The Zeng study collected urine samples of ranitidine users and tested the urine for NDMA. However, Zeng utilized GC-IT-MS for its analysis of urine samples. That test utilizes heat, and has been shown to cause residual ranitidine in the urine to form NDMA. Zeng was retracted on May 4, 2021 at the request of the authors: "[r]ecent research (1) has identified the potential for an analytical artefact associated with the use of gas chromatography that could have contributed to the levels of N-nitrosodimethylamine (NDMA) measured in urine samples containing ranitidine in this study. Given this artefact, the authors have informed the journal that their NDMA measurements are not reliable."[76]

On September 13, 2019, the FDA recommended the use of liquid chromatography with high resolution mass spectrometer (LC-HRMS) to measure levels of NDMA in ranitidine drug products, because gas chromatography (GC) based methods had been observed to elevate NDMA levels in tested materials.[77] On October 2, 2019, the FDA released a statement indicating that testing by LC-HRMS has shown the presence of much lower levels of NDMA in ranitidine.[78,79] On November 1, 2019, the FDA issued "Statement on new testing results, including low levels of impurities in ranitidine drugs." The statement indicated, "we have found levels of NDMA in ranitidine that are similar to the levels you would expect to be exposed to if you ate common foods like grilled or smoked meats. We also conducted tests that simulate what happens to ranitidine after it has been exposed to acid in the stomach with a normal diet and results of these test indicate that NDMA is not formed through this process. Similarly, if ranitidine is exposed to a simulated small intestine environment, NDMA is not formed." The FDA also stated that "[a]lthough many of these levels of NDMA observed through FDA testing are much lower than the levels some third-party scientists first claimed, some levels still exceed what the FDA considers acceptable for these medicines [96 nanograms of NDMA]."[80] The FDA tested various doses of ranitidine from eleven companies, three of which did not exceed 96 nanograms of NDMA.[81] None exceeded 1 microgram.[82] Thus, the study population included an unknown number of people who took uncontaminated valsartan. The Yoon study does not provide a compelling case to conclude that NDMA does not increase a human's risk of cancer when ingested at the levels seen with the contaminated valsartan.

III. Formation of Nitrosamines in the Valsartan API

As noted above, the formation of nitrosamines from secondary amines in the presence of nitrite and acid is absolutely basic organic chemistry. Any chemist who has taken even a basic organic chemistry course should know this. The test for a secondary amine was reaction with nitrite: a yellow oil, the nitrosamine, would be observed. A primary amine would produce bubbling due to the release of nitrogen from an unstable primary nitrosamine which rearranges to an unstable diazonium compound; a tertiary amine would not react (later shown to be not completely correct). Decades of research and volumes of published material clearly demonstrate that nitrite can react *easily* with amines to produce carcinogenic nitrosamines. The International Agency for Research on Cancer held international symposia on this issue every 2 – 3 years from the 1970s through the 1990s. The proceedings of these symposia are all available on the IARC website and describe hundreds of experiments demonstrating the ease of formation of carcinogenic nitrosamines in various settings including in chemical and drug manufacturing. For example, "It has been known since 1865 that the reaction of dimethylamine hydrochloride with sodium nitrite at an acidic pH yields *N*-nitrosodimethylamine."[83] Furthermore, the formation of nitrosamines in food cured with nitrite such as hot dogs and lunch meats has been extensively studied and documented. The U.S. Food and Drug Administration held regular meetings and symposia on this topic resulting eventually in significant decreases in the amounts of nitrite added to foods as a preservative. Volumes of research on nitrosamine contamination of various foods and tobacco products have been published. As set forth above, the FDA, ICH, and the EMA have all recognized the potential for nitrosamine impurities to exist in pharmaceuticals and the attendant risks. A qualified organic chemist in industry would be aware of this literature.

1. Nitrosamines in the ZHP API

I discuss the ZHP contamination in detail here to illustrate the root cause and the easy avoidability of the contamination. Ultimately, the manufacturers ignored basic chemistry principles, whether the root cause was reactions in the manufacturing process and/or cross-contamination due to solvent recovery or inadequate cleaning of equipment. The introduction of NDMA and NDEA into ZHP's Valsartan API was easily foreseeable. The Change Request Form for the Process Change for Valsartan Process II prepared on May 19, 2011, with an effective date of June 15, 2011[84] described the chemical processes, which included the addition of the solvent DMF, which was well known to decompose/degrade forming dimethylamine. "DMF decomposes slightly at its boiling point to afford dimethylamine and carbon monoxide, this reaction occurring even at room temperature in the presence of some acidic or basic materials."[85] "DMF ... Decomposes slightly at its normal boiling point to give small amounts of dimethylamine."[86]

There are multiple references in the Change Request Form to the need for process and method validation, and a reference to the need for testing including, "The residue of ZnCl2, and residue of solvents used in the process need to be tested for quality review." (Section 3). Unfortunately, from an organic chemistry perspective, ZHP failed to adequately evaluate the chemical processes, and failed to account for the risk of nitrosamine contamination. As a result, their risk assessment was inaccurate, i.e. "After evaluation, this change has a lower risk in terms of quality and safety,"[87] and "Synthetic route, intermediates remain the same and no adverse change in qualitative and quantitative impurity profile."[88] From the perspective of organic chemistry, as discussed herein and as recognized in ZHP's own root cause investigation (See ZHP Deviation Investigation Reports, ZHP00007221, PRINSTON0073443, PRINSTON0075797, PRINSTON0076100), a scientifically reasonable assessment of the Process Change would have identified the risk of formation of nitrosamine impurities, would have presumably led to testing for nitrosamines, and would have confirmed the formation was occurring. In addition, from an organic chemistry perspective this Change met the definition of a "Critical Change – A change which has direct or potential impact on product identity, strength, quality, purity and regulation, or have impact on validated Procedure, method, qualification or equipment."[89] This was a critical change because the process change had the foreseeable capacity to create, and resulted in, dangerous NDMA contamination. This analysis applies as well to the change from the TIN process to the TEA process with sodium nitrite quenching, which resulted in the formation of NDEA and NDMA. In light of the known potential results of the chemical processes, identification of the clearly foreseeable NDMA and NDEA impurity contamination could have been easily accomplished.

ZHP was certainly aware of the presence and significance of impurities in Valsartan API from the early days of their development of the original manufacturing process for Valsartan. For example, ZHP's knowledge of the significance of potential impurities was documented in the peer reviewed medical literature in 2006.[90] The article begins with a statement of the fundamental principle at the core of this litigation, that "The quality and safety of pharmaceuticals can be significantly affected by the presence of impurities. Consequently, the testing and establishment of limits for impurities in active pharmaceutical ingredients have become important initiatives by government and the pharmaceutical industry." The article, which included a co-author identified as an employee of ZHP, discussed available technologies for the detection and identification of impurities in API, in this instance Valsartan API.

Once the presence of NDMA was discovered, it was not difficult to determine the root cause. A July 27, 2017 email within ZHP refers to the root cause, specifically the fact that NDMA was known to occur in valsartan as a result of the use of sodium nitrite in the sodium azide quenching process, and that there was a need for, "the optimization of the valsartan sodium azide quenching process."[91] Dr. Li also confirmed that this was known to be a "common problem in the production and synthesis of Sartan APIs."[92] ZHP similarly concluded in a June 2018 document

summarizing the purported first detection of, and establishment of the root cause of the NDMA contamination, "this impurity is most likely generated during the 'azide quenching' by nitrous acid of the API manufacturing process."[93] The use of nitrite to decompose the azide reactant in the Valsartan synthesis process was a significant error due to the risk of nitrosamine formation, which should have been recognized. The use of nitrite should have raised a gigantic ***RED FLAG*** that nitrosamines could be present in the API. The same applies to the TEA process with sodium nitrite quenching.

Analysis of the Valsartan batches manufactured by ZHP with the zinc chloride process showed the presence of an unknown peak eluting just after toluene in the GC-MS analysis. On June 6, 2018, ZHP customer Novartis, which had contracted for further analysis of this API, notified ZHP that the unknown peak had been identified as NDMA. ZHP noted its failure to account for nitrosamines: "By looking into our CEP documents, it shows that NDMA is **not part of the controls in the current approved specifications** of the drug substance," and "Due to the fact that NDMA is a recently found **unexpected impurity** with the nature of probable carcinogen, and in order to understand the root cause for the occurrence of this impurity, ZHP has initiated root cause investigation."[94] It is important to note that ZHP's repeated statements that the NDMA was not known until June 2018 are contradicted by the July 27, 2017 email discussed herein, which not only references the fact that there was NDMA in the valsartan, but also the root cause tied to the sodium nitrite quenching.

The documents from ZHP clearly demonstrate how the formation of NDMA could have been avoided. They identified three critical factors: 1) use of dimethyl formamide in the tetrazole formation step, and the dimethyl formamide may have contained trace amounts of dimethylamine or the dimethylamine was formed during the process; 2) quenching of azide using nitrous acid (formed from nitrite under acidic conditions); and 3) quenching takes place in the presence of the product. ZHP concluded that NDMA was formed only when all 3 factors were present, based on extensive analysis by ZHP. Factor 2 should have raised a ***RED FLAG*** for the potential formation of nitrosamines. The contamination of dimethyl formamide with dimethylamine or the formation of dimethylamine during the process was foreseeable, and should have been evaluated. Factor 3 was shown to be critical to the problem; when the extraction of the product was performed prior to the addition of nitrite to quench the azide, no NDMA was observed, whereas in their original process, all samples were contaminated with NDMA. The results of the three factor analysis are perfectly clear and demonstrate a massive disregard for potential nitrosamine formation. Extraction prior to quenching would have been a simple remedy for the problem and should have been pursued. In their analyses of the product, they would not have identified NDMA in the chromatograms unless they were specifically looking for it, because the peaks would be too small. *But that is not a legitimate scientific excuse: ZHP should have been actively looking for nitrosamines based on the discussion above.* They could have used nitrosamine-selective methods such as combined gas chromatography-mass spectrometry for

this analysis. Using this or related methods, the detection of NDMA would have been straightforward.[95]

Prior to the process change from the "Process II" process to the Zinc Chloride process, which replaced Triethylamine with Zinc Chloride for the Tetrazole Ring Formation, and also replaced the original reaction solvent Toluene, with DMF (Dimethylformamide) and MTBE (Methyl tert-butyl ether), NDEA was similarly formed when 3 factors were present: 1) trimethylamine used as a catalyst for tetrazole formation; 2) nitrite used for decomposition of excess sodium azide; and 3) both factors 1 and 2 are together with the crude product. Lower amounts of NDEA were also formed due to trace amounts of diethylamine present in the trimethylamine used as a catalyst in the tetrazole formation step, and/or by direct nitrosation of trimethylamine. All of this was foreseeable, and if considered and tested for, the NDEA contamination would have been detected.

In the FDA inspection of ZHP,[96] numerous deficiencies were found, including 1)inadequate change control system; 2)inadequate validation program; 3)insufficient investigation of critical deviations; 4) the quality unit does not always fulfill the responsibilities of the quality unit; 5)cleaning procedures do not have sufficient detail; 6) equipment is not always of appropriate design;7)preventive maintenance procedures are not always adequate; 8) lubricants, heating fluids and coolants are not always food grade lubricants and oils; 9) sampling plans are not always scientifically sound; 10) stability studies are not always adequate; and 11) production deviations are not always thoroughly investigated. These deficiencies indicate a general disregard for potential problems in the manufacturing process, including the formation of nitrosamines. The report notes that while there is a procedure for investigating "out of specification/out of trend" deviations in the analysis of the product, it apparently is inconsistently applied.

In the specific investigation here, a peak eluting after the solvent toluene was ultimately definitively identified by an outside laboratory, using combined gas chromatography-mass spectrometry (GC-MS), as NDMA. The initial investigations disclosed by ZHP did not detect this peak due to errors in the headspace analysis process by its contractor, Zhejiang Haotian Testing and Technology Service, in which the vial was improperly crimped leading to non-detection of NDMA and any other peak.[97] This is apart from ZHP's confirmed knowledge at least as of July 2017 that there was NDMA in the valsartan.[98] The 5290 batches manufactured between 2016-2018 were reported to have contained an average of 57-64 parts per million of NDMA.

ZHP NDMA AND NDEA LEVELS:

The NDMA contamination levels confirmed in ZHP's contaminated valsartan were reported to range from 3.4 to 120 ppm, with variation between the East Zone and West Zone of the manufacturing facility, likely based on variations in the

production processes.[99] Additional documents establish even higher contamination levels.

In a document titled: Response to DMF Information Request Letter, ZHP provided the FDA with NDMA test results on residual solvents from three validation batches, as well as the NDMA Test Results for Batches Manufactured Using the ZnCl2 Process, presented as a chart of the results of testing of 783 batches manufactured between 12-28-2011 and 5-23-2018, with NDMA levels as high as 188.1 ppm.[100] These levels could have been established, for example using GC-MS, throughout the time that ZHP manufactured the valsartan API. This is demonstrated by the ease with which Novartis was able to identify NDMA. The same applies to the triethylamine manufacturing process with sodium nitrite quenching. In the Response to DMF Information Request Letter, ZHP reported NDMA levels for 55 batches that had been tested as of September 1, 2018, as high as 73.9 ppm.[101]

A separate spreadsheet provided by Solco to the FDA also documented the test results for the ZHP valsartan API batches manufactured with the zinc chloride process which were used to manufacture ZHP's finished dose for sale to Solco to be distributed in the United States, as well as the levels established by ZHP for the finished dose. There are a small number of batches with results in the single digits, with the lowest at 3.4 ppm, and the majority of the remaining batches have levels up to 188.1 ppm.[102] For context, 3.4 ppm translates to 1088 ng in a 320 mg pill, and 188.1 ppm translates to 60,192 ng in a 320 mg pill.

The ZHP Deviation Investigation Report dated November 11, 2018, titled Investigation regarding unknown impurity (genotoxic impurity) of Valsartan API (TEA process), provides NDEA levels for the TEA process valsartan API.[103] Testing of six validation batches established NDEA results of 0.03, 5.33, 12.77, 13.60, 18.83, and 13.51 ppm.[104] A separate table in that Report provides ranges and averages for the testing of 85 batches manufactured with the TEA process, documenting a range of 0.03-42.14, and average of 13.46, presumably in ppm. That table also sets forth NDEA levels in 111 batches manufactured with the zinc chloride process, documenting a range of 0-4.23 and average of 0.18, presumably in ppm.[105] As stated, since these impurities resulted from the manufacturing processes, all batches should be assumed to have been similarly contaminated, including those not tested.

Since we know that all batches of valsartan API manufactured with the zinc chloride process were contaminated with NDMA, the NDEA contamination would be additive and therefore further increase the risk of cancer for each pill manufactured from those batches. The TEA Deviation Investigation Report indicates that the likely cause of the NDEA contamination in the valsartan API manufactured with the zinc chloride process was cross-contamination due to shared equipment and solvent recovery.[106]

The aforesaid contamination of ZHP's valsartan API with nitrosamines including NDMA and NDEA, which are potent mutagenic carcinogens, resulted in an

unacceptable increased risk of cancer for those taking the medication. Thereafter, when aberrant peaks demonstrated unaccounted for impurities, the nitrosamine contamination could have been easily discovered based on knowledge of the potential chemical reactions and application of GC-MS to identify potential NDMA/NDEA. This was identified by Novartis even without the full information available to ZHP.[107] These failures and the consequent contamination of the Valsartan API resulted in the dangerous and unreasonable risk of causing or increasing the risk of causing cancer for those who ingested the contaminated valsartan with the reported levels of NDMA and NDEA.

No level of NDMA or NDEA in a pharmaceutical drug is "safe," in the sense that every exposure increases the risk to some incremental extent that one will develop cancer. The FDA set limits once the valsartan contamination was disclosed, and the aforesaid levels exceed the 96 nanogram/0.3 parts per million daily limit (based on 320 mg tablets) applied by the FDA to NDMA, and the 26.5 nanogram/.083 parts per million daily limit (based on 320 mg tablets) applied by the FDA to NDEA.[108] Those who ingested the contaminated valsartan above those levels sustained the unreasonably dangerous and unacceptable risk that this would cause or substantially contribute to causing cancer as a result of the NDMA and NDEA contamination.

It is important to note that the FDA's short term decision to delay the recall of the contaminated valsartan for a very brief period of time was not an endorsement of the safety of the medication.[109] Instead, this was the result of concern over the availability of the medication due to the widespread contamination, and a balancing of the risk of cancer against the more immediate risk of heart attack, stroke, or other life threatening results of a person abruptly ceasing the use of their hypertension medication.

2. Nitrosamines in the Hetero API

Hetero utilized a zinc chloride/DMF/sodium nitrite quenching process that was materially the same as ZHP's zinc chloride process, and the root cause of the NDMA impurity contamination of Hetero's valsartan was the same.[110] The reason for this occurring was the same as with ZHP. Mr. Ramarao confirmed this when he agreed with the following: "the most important problem" was that Hetero Unit 1 (API manufacturer) and Unit 5 (finished dose manufacturer) "never even realized the possibility that NDMA could form, so it was never actually looked for. That's the fundamental problem, correct?"[111]

The NDMA levels found on testing of Hetero's valsartan API manufactured with the zinc chloride process were confirmed in deposition testimony to range from 0.83 ppm to 7.78 ppm. This data was based on the testing of six batches, and was confirmed to be "representative of the contamination levels across the API – the Valsartan API that was sold from Unit 1 to Unit 5 and then sold in the United States."[112] As stated, since these impurities resulted from the manufacturing

process, all batches should be assumed to have been similarly contaminated, including those not tested.

These contamination levels caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting the valsartan manufactured by ZHP.

3. Nitrosamines in the Aurobindo API

Aurobindo manufactured valsartan API for sale in the United States using a process referred to as the Toluene route, according to deposition testimony from Sanjay Singh, Associate President of North American Technical Operations.[113] The nitrosamine contamination of Aurobindo's valsartan API resulted from cross-contamination caused by a solvent vendor, Lantech. [114] The root causes of this cross-contamination included (1) a contaminated plate in a vertical heat exchanger that was shared between Aurobindo and Mylan, among others,[115] and caused residue to build up and carry over from batch to batch, causing NDEA contamination in the tri-*n*-butyl tin chloride[116] (Aurobindo's Chief Quality Officer analogized this to a dirty microwave),[117] (2) shared tanks (between Aurobindo, Mylan, and others) that were used to store the tri-*n*-butyl tin chloride resulting in NDEA contamination,[118] and (3) Lantech supplied the fresh solvent ethyl acetate which contained TEA,[119] and during the manufacturing process the TEA reacted with nitrosyl chloride, a byproduct of Aurobindo's API manufacturing process, resulting in NDEA contamination.[120]

Both NDMA and NDEA were detected in the valsartan API utilized by Aurobindo. The reported levels of NDEA ranged from 0.028 ppm to 1.508 ppm.[121] The levels of NDMA ranged from below .1 ppm to .129 ppm, and were additive to the NDEA levels, where present.[122] Assuming the same solvent related practices were utilized with both the tested and untested batches, all batches should be assumed to have been similarly contaminated, including those not tested.

These contamination levels caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting the valsartan manufactured by ZHP.

4. Nitrosamines in the Mylan API

Mylan was vertically integrated and supplied valsartan API to Mylan's finished dose manufacturing facilities, and also supplied valsartan API to its sole external United States finished dose customer, Teva.[123] Mylan's root cause investigation found that NDEA was created in the solvent recovery process for o-xylene, the recovery layer of which contained traces of diethylamine and triethylamine, when it was recovered with nitrous acid, and carried over to the final API.[124] Mylan acknowledged that it was warned by its supplier as early as 2014 to

"avoid … nitrosating agents" with TEA due to the "possibility of formation of nitrosamines with nitrites or other nitrosating agents."[125]

Mylan confirmed that NDEA was present in every single API batch.[126] Mylan's API testing confirmed NDEA contamination in every API batch released to the US market, with levels between 0.1 ppm to 1.57 ppm.[127] Dr. Walt Owens, current Head of Global Regulatory Affairs and former Head of Global Quality, testified that "the API and finished dosage form [nitrosamine testing] results were essentially the same, you would be able to test the API alone."[128] Mylan's testing also showed that the valsartan API contained sporadic levels of NDMA contamination, in addition to the NDEA, including BQL, BDL, and from 0.01 ppm to 0.09 ppm.[129]Assuming the same solvent related practices were utilized with both the tested and untested batches, all batches should be assumed to have been similarly contaminated, including those not tested.

These contamination levels caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting the valsartan manufactured by ZHP.

5. Nitrosamines in the Finished Dose Formulations

The NDMA and NDEA levels would be expected to be the same or nearly so in the finished dose formulations incorporating the contaminated valsartan API. This was addressed and confirmed in the deposition of Hai Wang, the President of Solco, ZHP's wholly owned distributor in the United States. Hai Wang confirmed that this was determined by ZHP and that data was provided to the FDA.[130] Both ZHP and Hetero were vertically integrated thus the above discussion of the causes and levels of the nitrosamine contamination of the API addresses the NDMA and NDEA contamination in their finished dose formulations as well.

Finished dose manufacturers Teva and Torrent obtained valsartan API from API manufacturers and then incorporated it into their finished dose formulations.

6. Nitrosamines in the Teva Finished Dose Formulation.

Teva manufactured and sold finished dose valsartan utilizing ZHP manufactured valsartan API, and Mylan manufactured valsartan API, labeled either as Teva or Actavis.[131] The valsartan finished dose labeled as Actavis and sold in the United States initially was manufactured using ZHP TEA process with sodium nitrite quenching valsartan API, and then ZHP zinc chloride process valsartan API beginning in late-2014.[132] The valsartan finished dose labeled as Teva was manufactured using Mylan valsartan API.[133]

ZHP reported NDMA levels to Teva between 0.8 ppm and 240.1 ppm.[134] Teva also tested 83 batches of ZHP valsartan API with NDMA levels of 30.01 ppm to 221.63 ppm.[135] In addition, Teva tested six batches of its finished dose valsartan

manufactured with ZHP valsartan API with NDMA levels of 14.8 ppm to 31.3 ppm.[136] It was confirmed that all ZHP valsartan API sold to Teva contained NDMA in excess of 0.3 ppm.[137] Daniel Barreto, Teva's former Senior Vice President Global Quality Compliance, testified that the finished dose product would have the same levels of NDMA as tested in the API and Teva "extrapolate[d] the nitrosamine test results of the API to the valsartan finished dose." [138]

Teva also tested for NDEA. Teva initially tested eleven batches of Mylan valsartan API and ten of the eleven batches had NDEA levels above 0.08 ppm, from 0.09 ppm to 0.50 ppm.[139] Teva tested 26 additional batches of Mylan valsartan API and twenty-four of the twenty-six batches tested above .08 ppm for NDEA, with results ranging from 0.08 ppm to 0.42 ppm.[140] Since the contamination occurred at the level of the API suppliers, the untested batches would be expected to have the same or very similar contamination levels as the tested batches, as discussed above.

These contamination levels caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting the valsartan sold by Teva.

7. Nitrosamines in the Torrent Finished Dose Formulation.

Torrent purchased valsartan API from ZHP that was manufactured using the TEA with sodium nitrite quenching process. This was the only manufacturing process for ZHP valsartan API that was documented as being sold in the United States by Torrent.[141]

On August, 3, 2018, ZHP notified Torrent of "trace" amounts of NDMA in the Valsartan API sold to Torrent, which was the API manufactured using the ZHP TEA process with sodium nitrite quenching (as discussed above).[142] On Sept 7, 2018, ZHP notified Torrent that what ZHP described as, "another contaminant, NDEA, has been detected in the finished dose batches of valsartan."[143]

The levels of NDMA found on testing of the valsartan API purchased by Torrent from ZHP and then incorporated in its finished dose formulation sold in the United States were reported to range from 0.37 parts per million to 125.15 parts per million.[144] The levels of NDEA were found to range from 0.23 ppm to 16.93 ppm, with several batches found to be BDL and BQL range (Below Detection Limit and Below Quantification Limit).[145] All batches had NDMA and the majority had both NDMA and NDEA, which would increase the cancer risk. Since the contamination occurred at the level of the API supplier, ZHP, the untested batches would be expected to have the same or very similar contamination levels as the tested batches, as discussed above.

These contamination levels caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting the valsartan sold by Torrent.

IV. Conclusion

The contamination of the valsartan API, and consequent contamination of the valsartan finished dose, as described above, caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting the valsartan. As described above, a range of cancers have been associated with intake of NDMA (and NDEA by extension). In general, the increased risk would likely be commensurate with the contamination levels, dosages, and periods of use. Therefore, people who ingested the valsartan with higher contamination levels and larger doses, over longer periods of time, would likely have a more substantial increased risk as opposed to those who ingested valsartan with lower contamination levels and lower doses, and for shorter periods of use. However, even those lower levels, lower dosages, and shorter periods of use present an unreasonable danger and risk, a risk to which one would not knowingly or deliberately expose a person.[146]

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[138] Daniel Barreto Dep. Tr. 4/14/2021, 201:23-202:9; 275:9-276:5; 367:9-368:2.
[139] TEVA-MDL2875-00048605, at 61 of 61.
[140] *Ibid.*, 58-59.
[141] TORRENT-MDL2875-00072650; Sushil Jaiswal Dep. Tr. 6/04/20211, 67:21-24, 68:1-7.
[142] TORRENT-MDL2875-00131255; Reddy Neravetla Dep. Tr. 5/26/2021, 102:2-21.
[143] TORRENT-MDL2875-00504834; Jocelyn Rivera Dep. Tr. 02/22/2021, 438:5-24; Dawn Chitty Dep. Tr. 5/13/2021, 349:13-24, 350:1-4.
[144] TORRENT-MDL2875-00366172; Sushil Jaiswal Dep. Tr. 6/04/2021, 64:5-22, 65:7-24, 71:7-23, 86:17-24, 87:1-19.
[145] TORRENT-MDL2875-00135398; Dawn Chitty Dep. Tr. 5/13/2021, 59:15-24, 61:14-18.
[146] As recognized above, the FDA allowed contaminated valsartan to remain available for a short time in order to ensure there would not a shortage of this blood pressure medication in the short term. This decision was not an indication that the ingestion of the contaminated valsartan was considered to be safe or desirable.

Exhibit 1

Stephen S. Hecht, Ph.D.

Winston R. and Maxine H. Wallin Land Grant Professor of Cancer Prevention
American Cancer Society Professor, American Chemical Society Fellow
Masonic Cancer Center, University of Minnesota, Minneapolis, MN 55455

Education

Duke University, B.S. (with honors), Chemistry – 1964
Massachusetts Institute of Technology, Ph.D., Organic Chemistry – 1968

Professional Experience

Masonic Cancer Center, University of Minnesota, Minneapolis, MN

- Wallin Land Grant Professor of Cancer Prevention and Professor, Department of Laboratory Medicine and Pathology, 1996-present
- Head, Carcinogenesis and Chemoprevention Program, 1998-2014
- Member, Medicinal Chemistry and Pharmacology Graduate Programs, 1996-present

American Health Foundation, Valhalla, NY

- Director of Research, 1987-1996
- Chief, Division of Chemical Carcinogenesis, 1980-1996
- Head, Section of Organic Chemistry, Division of Environmental Carcinogenesis, 1973-1980

United States Department of Agriculture, Philadelphia, PA

- National Research Council Fellow, 1971-1973

Haverford College, Haverford, PA

- Assistant Professor of Chemistry, 1969-1971

Massachusetts Institute of Technology, Cambridge, MA

- Postdoctoral Fellow, Mass Spectrometry, Professor Klaus Biemann, 1968-1969

Honors and Awards

Academy for Excellence in Team Science, University of Minnesota, 2019
Listed in AACR Landmarks in Cancer Research, 2017: Tobacco-Specific Nitrosamines, *JNCI* 60: 819-824 (1978)
University of Minnesota Medical School Dean's Distinguished Research Lectureship, 2017
American Chemical Society Minnesota Section, Minnesota Award, 2017
University of Minnesota Medical School Wall of Scholarship, 2015
Elected American Association for the Advancement of Science Fellow, 2014
Selected as next Editor-In-Chief, *Chemical Research in Toxicology*, American Chemical Society, 2012
Joseph Cullen Award, American Society of Preventive Oncology, 2012
Elected American Chemical Society Fellow, 2009
Founders' Award, Division of Chemical Toxicology, American Chemical Society, 2009
Academy for Excellence in Health Research, Academic Health Center, University of Minnesota, 2006
American Association for Cancer Research-Cancer Research and Prevention Foundation Award for Excellence in Cancer Prevention Research, 2006
Merit Award, National Cancer Institute, 2004-2014
Dr. William Cahan Distinguished Professor Award, Flight Attendant Medical Research Institute, 2002
Alton Ochsner Award Relating Smoking and Health, 2001
American Cancer Society Research Professor, 2000-2009

Wallin Chair in Cancer Prevention, Masonic Cancer Center, University of Minnesota, 1996-
Endowed Chair in Carcinogenesis and Chemoprevention, American Health Foundation, 1992-1996
Cancer Research Covers: March 1, 1988; February 15, 1993
Chemical Research in Toxicology Covers: June 1998, July 2007, February 2011
Cancer Epidemiology Biomarkers & Prevention Cover, December 2003
Outstanding Investigator Grant, National Cancer Institute, 1987-2001
Research Career Development Award, National Cancer Institute, 1975-1980
National Research Council Fellow, 1971-1973
Phi Beta Kappa, 1964

Current Research Interests

- Mechanisms and prevention of tobacco-induced cancer
- Carcinogen biomarkers and their application in molecular epidemiology and cancer prevention
- Mechanisms of chemical carcinogenesis in humans
- Chemoprevention of cancer

Selected Active Grant Support

Principal Investigator
Continually funded by the U.S. National Cancer Institute since 1975

- NCI, CA-81301, Metabolism of Carcinogenic Tobacco-Specific Nitrosamines, 1999-
- NCI, CA-203851, e-Cigarettes: Formaldehyde DNA Adducts, Oxidative Damage, and Potential Toxicity and Carcinogenesis, 2017-
- NCI, CA-222005, Clinical Trial of Watercress in Detoxification of Environmental Toxicants and Carcinogens, 2018 -
- NCI, CA-138338 (P01), Mechanisms of Ethnic/Racial Differences in Lung Cancer due to Cigarette Smoking, 2010 -

Co-Principal Investigator
NIEHS, U2CES26533, Minnesota CHEAR Exposure Assessment Hub

Selected Professional Activities

Peer Review
AACR-Johnson & Johnson Lung Cancer Innovation Science Grants Committee, 2017-2019
NIH Center for Scientific Review Special Emphasis Panel, Member 2020; Chair, 2019
NIH Cancer Prevention Study Section, ad hoc, 2018
Special Emphasis Panel, NCI PREVENT Cancer Program, 2011 –
NIEHS Childrens' Health Exposure Analysis Resource Access Committee, 2017 -
Special Emphasis Panel, NCI SPORE grants, 2015
Council for Extramural Grants, American Cancer Society, 2010-2014
Chair, Chemo/Dietary Prevention Study Section, National Institutes of Health 2006-2009
Board of Scientific Counselors, Subcommittee 2, Basic Sciences, National Cancer Institute, 2001-2004
Peer Review Committee on Carcinogenesis, Nutrition, and the Environment, American Cancer Society, 1998-2001; Chair, 2001
Grants Review Panel, American Institute for Cancer Research, 1984-1987
Chemical Pathology Study Section, National Institutes of Health, 1981-1985

Ad Hoc Reviewer:
National Cancer Institute, Cancer Center Support Grant Program

National Institute of Environmental Health Sciences
Dutch Cancer Society
Florida Department of Health
Alberta Heritage Foundation for Medical Research
Veterans Administration
New Jersey Commission on Cancer Research
United States - Israel Bi-national Science Foundation
California Tobacco Related Disease Research Program
Ohio Cancer Research Associates

Selected Advisory Groups and Related Activities

European Food Safety Authority, Contamination Working Group on N-Nitrosamines in Food, 2021
National Research Council Committee on Health Effects and Patterns of Use of Premium Cigars, 2021
U.S. Food and Drug Administration Panel on N-Nitrosamines in Pharmaceutical Products, 2021
Panel Member, 2018 American Cancer Society Professors' Meeting Discussion: "Bad luck" hypothesis
Member (ad hoc), Tobacco Products Scientific Advisory Committee, FDA, 2018
Reviewer, U.S. National Academies, Public Health Risks and Benefits of e-Cigarettes, 2017
Nomination Committee, Division of Chemical Toxicology, American Chemical Society, 2017-2019
Expert Consultation on the Integrated Exposure-Response Function, Univ. of Washington, 2017
Data Safety and Monitoring Board: NHLBI HAPIN study, Household Air Pollution and Health, 2017-
Chair, Nominating Committee, American Chemical Society Sosnovsky Award for Cancer Research, 2014
International Agency for Research on Cancer Monographs Program, Peer Review Committee, 2014
Frontiers in Cancer Prevention Annual Meeting, Program Committee, 2013
Round Table Meeting of the Senate Commission on Food Safety of the German Research Foundation: Nitrate and Nitrite in the Diet, Bonn, Germany, 2012
International Agency for Research on Cancer, Workshops on Tumor Concordance and Meshansims of Carcinogenesis, Lyon, France, 2012
Institute of Medicine, Committee on Scientific Standards for Studies on Reduced Risk Tobacco Products, 2011
AACR Cancer Prevention Committee and Cancer Prevention Summit, 2016
Tobacco Constituents Subcommittee, TPSAC, U.S. Food and Drug Administration, 2010
Flavor and Extract Manufacturers Association Expert Panel, 2010-
AACR Task Force on Tobacco and Cancer, 2009- 2012
External Advisory Board, University of Illinois Cancer Center, 2010-2014
Advisory Committee, Translational Cancer Research Center, South Dakota State University, 2009-2014
Chair-Elect to Past Chair, Chemistry in Cancer Research Working Group, AACR, 2007-2009
Chair, Program Committee, AACR Conference, Chemistry in Cancer Research: A Vital Partnership, 2007
Member, NCI-SRNT FDA Tobacco Regulation Legislation Review Project, 2009
International Agency for Research on Cancer, Knowledge Synthesis in Gene-Environment Interactions in Cancer, Lyon, France, 2009
Strategic Dialogue on Tobacco Harm Reduction, 2006-2007
Committee on Defining Upper Limits for Tobacco Toxicants, WHO TobReg, 2006-2007
Chair, Scientific Advisory Board, Center for Excellence in Environmental Toxicology, University of Pennsylvania, 2005-2010
Chemistry in Cancer Research, AACR, Think Tank of Leaders in the Field, 2005
Chapter Editor for Cancer, Surgeon General's Report, How Cigarette Smoking Causes Disease, 2010
Contributor, Surgeon General's Report, Passive Smoking and Health, 2004; Health Consequences of Smoking, Fifty Years of Progress, 2014
Co-organizer, Symposium on Tobacco Carcinogenesis, American Chemical Society National Meeting, 2005
Program Committee Co-Chairperson, AACR Frontiers in Cancer Prevention Meeting, 2004, 2007

National Cancer Institute Carcinogenesis Think Tank, 2004
National Cancer Institute Biotechnology Initiative for Cancer Public Health Working Group, 2004
National Tobacco Monitoring, Research, and Evaluation Workshop, 2002
International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 37, *Tobacco Habits Other than Smoking*, 1985; Vol. 83, *Tobacco Smoke and Involuntary Smoking*, 2002; Vol. 85, *Betel Quid and Areca Nut*, Chair, 2003; Vol. 89, *Smokeless Tobacco and Some Related Nitrosamines,* 2004; Vol 100E, *A Review of Human Carcinogens-Lifestyle Factors*, 2009
International Agency for Research on Cancer Handbooks on Cancer Prevention, Vol. 9, *Cruciferous Vegetables, Isothiocyanates, and Indole-3-carbinol*, 2003
Lung Cancer Progress Review Group, Co-Chair, Chemoprevention Section, National Cancer Institute, 2001
Board of Scientific Counselors, National Toxicology Program, 1997-2001
Science Advisory Board, National Center for Toxicological Research, FDA, 1998-2002
Board of Scientific Counselors, Division of Cancer Etiology, National Cancer Institute, 1989-1995
Division of Chemical Toxicology, American Chemical Society, Chair, 1999-2000; Chair-elect, 1997-1998; Program Chair, 1996; Chair, Nominations Committee, 2011
Board of Directors, Minnesota Smoke Free Coalition, 1997-2001
Health Research Committee, Health Effects Institute, 1992-1996
External Scientific Advisory Board, Ohio State University Comprehensive Cancer Center, 2002-2006
Corporation Visiting Committee, Division of Bioengineering and Environmental Health, Massachusetts Institute of Technology, 2000-2003
External Advisory Committee, Environmental Health Sciences Center, Oregon State University, 1996-2000
Cancer Prevention Think Tank, American Cancer Society, 1995
American Association for Cancer Research Program Committee, 1983, 1990, 1993, 1997, 1999, 2000, 2003-2005, 2009 (co-chair), 2010; Session Chair, 1984, 1986, 1988, 1991, 200, 2003
Advisory Group, Center in Molecular Toxicology, Vanderbilt University School of Medicine, 1991-1997; Chair, 1995-1997
Advisory Panel, Inhalation Toxicology Research Institute, 1990-1996
Advisory Panels, Chemical Industry Institute of Toxicology, 1990-1996
Advisory Panel, NYU-Nelson Institute of Environmental Medicine, 1992-1995
Peer Review Committee-Scientific Council, International Agency for Research on Cancer, 1991
Upper Aerodigestive Cancer Working Group, National Cancer Institute, 1986-1989
Contributor, Surgeon General's Report on the Health Consequences of Using Smokeless Tobacco, 1986

Editorial Activities

Editor-in-Chief, *Chemical Research in Toxicology*, 2013 - 2017
Associate Editor, *Journal of Medicinal Chemistry*, 2004 - 2012
Associate Editor, *Nicotine and Tobacco Research*, 2009 - present

Editorial Boards:

Mutagenesis, 2014 - present
Cancer Research, 1980 - 2000; 2010 - 2012
Cancer Epidemiology, Biomarkers, and Prevention, 1990 - present
Molecular Cancer Therapeutics, 2001 - 2012
Cancer Prevention Research, 2008 – present
Journal of Environmental Science and Health, Part C, 2016 - present
Chemical Research in Toxicology, 1988 - 1990, 1992 - 1994, 2010 - 2012
Lung Cancer, 2001 - 2012
Cancer Letters, 1999 - 2006
Carcinogenesis, 1986 - 1990; 2001 - 2006

Chemico-Biological Interactions, 1992 - 1998
Mutation Research, 2002 - 2007
Clinical Cancer Research, 2007 - 2011

Selected Invited Lectures and Conferences, 2002-2019

Cancer Research Campaign, Manchester, England
State University of New York, Stony Brook
Society of Toxicology National Meetings
New York University
Virginia Piper Cancer Research Institute
Vanderbilt University
Reducing Tobacco Harm Conference, Washington, DC
Diet and Optimum Health, Portland, OR
American Cancer Society, Atlanta, GA
Mechanisms of Carcinogenesis and Xenobiotic Metabolism, Rutgers University
International Symposium on Polycyclic Aromatic Compounds
EMS Special Conference, Breast Cancer and Environmental Mutagens
Mayo Clinic, Rochester, MN
Biomarkers for Tobacco Exposure, Minneapolis
University of Wisconsin
Ohio State University
National Cancer Institute Chemoprevention Branch
Columbia University
Society for Research on Nicotine and Tobacco
East-West Conference on Tobacco and Alcohol
Tobacco Harm Reduction Network
Chemistry in Cancer Research
National Cancer Institute – Frederick
Evaluation of Smokeless Tobacco, Washington, DC
University of California, San Diego
AACR Frontiers in Cancer Prevention Meetings
AACR National Meetings
Society for Research on Nicotine and Tobacco
University of North Carolina
Hormel Institute
University of Pittsburgh
National Cancer Institute – Causes of Cancer
National Cancer Institute – Methods and Biomarkers
Roswell Park Cancer Center
Hanna Symposium, Univ. of Minnesota
New Jersey Governor's Conference on Cancer Prevention
American Chemical Society National Meetings
Dietary Factors and Cancer Prevention, Rochester, MN
Wadsworth Center, Albany, NY
University of Pennsylvania
University of Iowa
University of Louisville
University of Kentucky
3M Company, St. Paul, MN
Reducing Tobacco Use in Minnesota
Penn State, Hershey Medical Center
Northwestern University
MD Anderson Cancer Center (2)
University of Utah
Abbott Laboratories
Virginia Commonwealth University
Medical University of South Carolina
Environmental Mutagen Society, Puerto Rico
Dartmouth University
Toxicology Forum, Washington, DC
Tulane University
Indiana University
South Dakota State University
EOHSI, Rutgers University/UMDNJ
World Conference on Tobacco or Health, Mumbai
International Agency for Research on Cancer, Lyon
Ohio State University
University of Arizona Cancer Center
University of Oklahoma
UCLA Molecular Toxicology
University of Tennessee
Microsomes and Drug Oxidation, Beijing
University of Sao Paulo, Brazil
ETH, Zurich
Biomarkers Workshop, Műnster, Germany
Medical College of Wisconsin
Healthy Foods, Healthy Lives Symposium, Univ. of Minnesota
Japan Society of Clinical Oncology, Yokohama
Nitrate and Nitrosamines, Bonn, Germany
Gordon Research Conference Drug Metabolism, Keynote Speaker
Brown University
University of Rhode Island

Minnesota Department of Health
Beijing University of Technology
Peking University
National Center for Nanoscience and Technology, Beijing
U.S. Food and Drug Administration-e-Cigarettes
North Dakota State University
U.S. Food and Drug Administration-Biomarkers
Joint AACR/IASLC Meeting, San Diego
ETH, Zurich
IASLC Meeting, Vienna, Austria
University of Pittsburgh
Penn State Cancer Institute
King's College, London
American Association for Dental Research
Minnesota Department of Health
Kaohsiung Medical University, Taiwan

University Activities

Principal Lecturer and Organizer

Chemical Carcinogenesis and Chemoprevention, 3 credits, 1998 - 2003

Lecturer

Chemical Aspects of Drug Metabolism and Bioactivation
Advanced Pharmacology
Cancer Epidemiology
Molecular Epidemiology

Academic Program Memberships

Medicinal Chemistry Graduate Program
Pharmacology Graduate Program
Combined M.D./Ph.D. Program

Committees

Masonic Cancer Center: Executive Committee and Cancer Prevention and Control Steering Committee, 1998-2014
Masonic Cancer Center Space Committee, 2016 -
M.D./Ph.D. Program Steering Committee, 2000 - 2009

Memberships

American Association for Cancer Research
American Association for the Advancement of Science
American Chemical Society
American Society of Preventive Oncology
American Society for Mass Spectrometry
International Society for the Study of Xenobiotics
Society for Research on Nicotine and Tobacco
American Society for Pharmacology and Experimental Therapeutics

Selected Contributions to Science (with key references)

1. *Tobacco-specific nitrosamines: identification in tobacco products, carcinogenicity, metabolism, DNA binding, and biomarkers.* The tobacco-specific nitrosamines *N'*-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are considered to be important causes of tobacco-induced cancer. We carried out most of the carcinogenicity, metabolism, and DNA binding studies of NNN

and NNK, leading to a broad understanding of their uptake and metabolism in humans. We developed highly sensitive mass spectrometric methods for analysis of their metabolites in humans; the NNAL biomarker in particular has been widely used in multiple studies of tobacco-specific carcinogen exposure and risk for cancer. Our studies on NNAL in the urine of non-smokers exposed to secondhand smoke contributed to the clean indoor air now enjoyed nearly universally.

a. **Hecht, S. S.**, Carmella, S. G., Murphy, S. E., Akerkar, S., Brunnemann, K. D., and Hoffmann, D. (1993) A tobacco-specific lung carcinogen in the urine of men exposed to cigarette smoke. *N. Engl. J. Med.* 329, 1543-1546.

b. **Hecht, S. S.** (1998) Biochemistry, biology, and carcinogenicity of tobacco-specific N-nitrosamines. *Chem. Res. Toxicol.* 11, 559-603.

c. **Hecht, S. S.**, Stepanov, I., and Carmella, S. G. (2016) Exposure and metabolic activation biomarkers of carcinogenic tobacco-specific nitrosamines. *Acc. Chem. Res.* 49, 106-114. PMCID: PMC5154679

d. Li, Y., and **Hecht, S. S.** (2021) Identification of an *N*′-nitrosonornicotine-specific deoxyadenosine adduct in rat liver and lung DNA. *Chem. Res. Toxicol.* 34, 992-1003.

2. *Application of tobacco carcinogen and toxicant biomarkers in clinical and epidemiologic studies*. We developed a panel of urinary tobacco carcinogen and toxicant biomarkers, using state of the art high throughput liquid chromatography-mass spectrometric techniques, and have applied these methods in collaborative studies to explore human exposure and risk. Using samples from nested case-control studies within prospective cohorts, we demonstrated that NNAL, nicotine metabolites, and phenanthrene tetraol (a PAH metabolite) were significantly related to lung cancer and that NNN was significantly related to esophageal cancer. We further showed significant differences in levels of these metabolites in ethnic groups with differing risks for lung cancer, and have analyzed more than 60,000 urine samples for multiple biomarkers in a clinical study of the reduced nicotine cigarette.

   a. Yuan, J. M., Knezevich, A. D., Wang, R., Gao, Y. T., **Hecht, S. S.**, and Stepanov, I. (2011) Urinary levels of the tobacco-specific carcinogen *N*′-nitrosonornicotine and its glucuronide are strongly associated with esophageal cancer risk in smokers. *Carcinogenesis* 32, 1366-1371. PMCID: PMC3202311

   b. Park, S. L., Carmella, S. G., Ming, X., Stram, D. O., Le Marchand, L., and **Hecht, S. S.** (2015) Variation in levels of the lung carcinogen NNAL and its glucuronides in the urine of cigarette smokers from five ethnic groups with differing risks for lung cancer. *Cancer Epidemiol. Biomarkers Prev.* 24, 561-569. PMCID: PMC4355389

   c. Yuan, J. M., Nelson, H. H., Carmella, S. G., Wang, R., Kuriger-Laber, J., Jin, A., Adams-Haduch, J., **Hecht, S. S.**, Koh, W. P., and Murphy, S. E. (2017) *CYP2A6* genetic polymorphisms and biomarkers of tobacco smoke constituents in relation to risk of lung cancer in the Singapore Chinese Health Study. *Carcinogenesis* 38, 411-418. PMCID: PMC6248819

   d. Hatsukami, D. K., Luo, X., Jensen, J. A., al'Absi, M., Allen, S. S., Carmella, S. G., Chen, M., Cinciripini, P. M., Denlinger-Apte, R., Drobes, D. J., Koopmeiners, J. S., Lane, T., Le, C. T., Leischow, S., Luo, K., McClernon, F. J., Murphy, S. E., Paiano, V., Robinson, J. D., Severson, H., Sipe, C., Strasser, A. A., Strayer, L. G., Tang, M. K., Vandrey, R., **Hecht, S. S.**, Benowitz, N. L., and Donny, E. C. (2018) Effect of immediate vs gradual reduction in nicotine content of cigarettes on biomarkers of smoke exposure: a randomized clinical trial. *JAMA* 320, 880-891. PMCID: PMC6372240

3. *Metabolism and DNA adducts of PAH and aldehydes*. We carried out extensive studies on metabolism and DNA adduct formation by these compounds. The results of these studies were consistent with, expanded, and supported the bay region diol epoxide model of PAH carcinogenicity, leading us to develop the phenanthrene tetraol biomarker of PAH exposure plus metabolic activation, and to use high resolution mass spectrometry for analysis of benzo[*a*]pyrene-DNA adducts in the human lung. Our studies on

nitrosamine metabolism evolved to investigations of related metabolically formed aldehydes. Our group was the first to identify acrolein and crotonaldehyde-derived DNA adducts that have been extensively investigated, and we developed the first methods for reliable quantitation of formaldehyde and acetaldehyde-DNA adducts in humans. The latter are particularly relevant to alcohol consumption and its role in carcinogenesis.

a. Balbo, S., Meng, L., Bliss, R. L., Jensen, J. A., Hatsukami, D. K., and **Hecht, S. S.** (2012) Kinetics of DNA adduct formation in the oral cavity after drinking alcohol. *Cancer Epidemiol. Biomarkers Prev.* 21, 601-608. PMCID: PMC3319307

b. Villalta, P. W., Hochalter, J. B., and **Hecht, S. S.** (2017) Ultrasensitive high-resolution mass spectrometric analysis of a DNA adduct of the carcinogen benzo[*a*]pyrene in human lung. *Anal. Chem.* 89, 12735-12742. PMCID: PMC6027747.

c. Yang, J., Balbo, S., Villalta, P. W., and **Hecht, S. S.** (2019) Analysis of acrolein-derived 1,N^2-propanodeoxyguanosine adducts in human lung DNA from smokers and nonsmokers. *Chem. Res. Toxicol.* 32, 318-325. PMCID: PMC6644703

d. Chen, M., Carmella, S. G., Li, Y., Zhao, Y., and **Hecht, S. S.** (2020) Resolution and quantitation of mercapturic acids derived from crotonaldehyde, methacrolein, and methyl vinyl ketone in the urine of smokers and nonsmokers. *Chem. Res. Toxicol.* 33, 669-677. PMCID: PMC7193944

4. *Chemoprevention of cancer*. We applied our understanding of mechanisms of tobacco carcinogenesis to the identification of potential naturally occurring agents which could diminish the risk for cancer. This led to extensive studies on a variety of agents including isothiocyanates, indole-3-carbinol, *myo*-inositol, and related compounds. 2-Phenethyl isothiocyanate (PEITC), a potent inhibitor of carcinogenesis in several systems, was chosen for further development because of its natural occurrence and favorable preclinical profile. Together with our colleagues, we carried out an FDA-approved clinical trial of PEITC as an inhibitor of the metabolic activation of NNK in smokers, which showed modest inhibition, but a far greater effect on detoxification of common environmental agents such as benzene, a lead we are pursuing actively in a clinical trial of watercress, an abundant source of PEITC, to enhance detoxification of these agents.

   a. **Hecht, S. S.**, Trushin, N., Rigotty, J., Carmella, S. G., Borukhova, A., Akerkar, S. A., and Rivenson, A. (1996) Complete inhibition of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone induced rat lung tumorigenesis and favorable modification of biomarkers by phenethyl isothiocyanate. *Cancer Epidemiol. Biomarkers Prev.* 5, 645-652.

   b. **Hecht, S. S.**, Kassie, F., and Hatsukami, D. K. (2009) Chemoprevention of lung carcinogenesis in addicted smokers and ex-smokers. *Nat. Rev. Cancer* 9, 476-488. PMCID: PMC3876956.

   c. Yuan, J.-M., Stepanov, I., Murphy, S. E., Wang, R., Allen, S., Jensen, J., Strayer, L., Adams-Haduch, J., Carmella, S. G., Upadhyaya, P., Le, C., Kurzer, M., Nelson, H. H., Yu, M. C., Hatsukami, D. K., and **Hecht, S. S.** (2016) Clinical trial of 2-phenethyl isothiocyanate as an inhibitor of metabolic activation of a tobacco-specific lung carcinogen in cigarette smokers. *Cancer Prev. Res.* 9, 396-405. PMCID: PMC4854759.

   d. Yuan, J. M., Murphy, S. E., Stepanov, I., Wang, R., Carmella, S. G., Nelson, H. H., Hatsukami, D., and **Hecht, S. S.** (2016) 2-Phenethyl isothiocyanate, *glutathione S-transferase M1* and *T1* polymorphisms, and detoxification of volatile organic carcinogens and toxicants in tobacco smoke. *Cancer Prev. Res.* 9, 598-606. PMCID: PMC4930697

5. *Expertise in tobacco carcinogenesis*. I have served on multiple U.S. and W.H.O. committees evaluating the tobacco and cancer problem and recommending solutions, and have regularly contributed to U.S. Surgeon General Reports on tobacco and cancer. I have written numerous invited reviews and book chapters on

aspects of tobacco carcinogenesis. With Professor D. Hatsukami, I am currently editing a book entitled "Tobacco and Cancer: the Science and the Story" to be published in 2021 by World Scientific Press.

a. **Hecht, S. S.** (1999) Tobacco smoke carcinogens and lung cancer. *J. Natl. Cancer Inst.* 91, 1194-1210. (cited 1349 times).

b. **Hecht, S. S.** (2003) Tobacco carcinogens, their biomarkers, and tobacco-induced cancer. *Nature Rev. Cancer* 3, 733-744. (cited 883 times).

c. **Hecht, S. S.**, and Szabo, E. (2014) Fifty years of tobacco carcinogenesis research: From mechanisms to early detection and prevention of lung cancer. *Cancer Prev. Res.* 7, 1-8. PMCID: PMC4296669

d. **Hecht, S. S.** (2017) Oral cell DNA adducts as potential biomarkers for lung cancer susceptibility in cigarette smokers. *Chem Res Toxicol* 30, 367-375. PMCID: PMC5310195

Link to Bibliography Over 850 publications including more than 590 peer-reviewed journal articles and over 250 book chapters and related publications; control plus click to follow link **http://www.ncbi.nlm.nih.gov/sites/myncbi/stephen.hecht.1/bibliography/41146177/public/?sort=date&direction=ascending**

Stephen S. Hecht, Ph.D.

Bibliography

Table of Contents

Stephen S. Hecht, Ph.D.

Bibliography

Original Articles and Patents

1. Cope, A.C. and Hecht, S.S. Proximity Effects, XLVIII. Aprotic decomposition of 2-phenylcyclooctanone p-toluenesulfonylhydrazone and 3-phenylcyclooctanone p-toluenesulfonylhydrazone. *J. Am. Chem. Soc.*, **89**: 6920-6925, 1967.
2. Hecht, S.S. and Greene, F.D. Di-t-butyloxadiaziridine, the cyclic form of an azoxy group. Ring-chain isomerism in three-membered rings. *J. Am. Chem. Soc.*, **89**: 6761, 1967.
3. Greene, F.D. and Hecht, S.S. Cyclic azoxy compounds-relation of structural considerations to NMR spectra. *Tetrahedron Lett.*, **7**: 575-578, 1969.
4. Greene, F.D. and Hecht, S.S. Oxadiaziridines, the cyclic form of an azoxy group. Synthesis, valence isomerism, and reactivity. *J. Org. Chem.*, **35**: 2482-2486, 1970.
5. Hecht, S.S. Alkylation of metal derivatives of 1,3-diphenyl-1,3-propanedione with 1,2-diphenyl-3,3-dichlorocyclopropene. *Tetrahedron Lett.*, **50**: 4385-4388, 1970.
6. Hecht, S.S. Transannular carbene reactions; an intermediate organic laboratory experiment. *J. Chem. Ed.*, **48**: 340-341, 1971.
7. Hecht, S.S. Reaction of hydrazine with 1,2-diphenyl-3-dibenzoylmethylenecyclopropene and 1,2-diphenyl-3-diacetylmethylenecyclopropene; formation of pyridazines. *Tetrahedron Lett.*, **35**: 3731-3734, 1972.
8. Rothman, E.S., Hecht, S.S., Pfeffer, P.E., and Silbert, L.S. Enol Esters, XV. Synthesis of highly hindered esters *via* isopropenyl ester intermediates. *J. Org. Chem.*, **37**: 3551-3552, 1972.
9. Hecht, S.S. and Rothman, E.S. Amide hydrofluoroborates. *J. Org. Chem.*, **38**: 395-396, 1973.
10. Rothman, E.S., Moore, G.G., and Hecht, S.S. Enol Esters, XVII. Reactions of isopropenyl stearate with diethyl malonate, acetoacetic ester, and related keto esters. *J. Org. Chem.*, **38**: 2540-2543, 1973.
11. Hecht, S.S. and Rothman, E.S. Cleavage of saturated fatty acid amides by anhydrous hydrogen fluoride-boron trifluoride. *J. Org. Chem.*, **38**: 3733-3737, 1973.
12. Hecht, S.S., Bondinell, W.E., and Hoffmann, D. Chemical studies on tobacco smoke, XXIX. Chrysene and methylchrysenes: Presence in tobacco smoke and carcinogenicity. *J. Natl. Cancer Inst.*, **53**: 1121-1133, 1974.
13. Hoffmann, D., Hecht, S.S., Ornaf, R.M., and Wynder, E.L. Chemical studies on tobacco smoke, XXX. N'-nitrosonornicotine in tobacco. *Science*, **186**: 265-267, 1974.
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Chapters, Invited Articles, Books and Other Papers

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EXHIBIT 2
Documents Reviewed

ZHP Documents

1. ZHP00007221, Deviation Investigation Report regarding a Suspect Genotoxic Impurity of Valsartan, DCE-18001.
2. ZHP00004352, Deviation Report Form, Q/ZHH QA-079-1.
3. ZHP00013245, Deviation Investigation Report regarding a Suspect Genotoxic Impurity of Valsartan, DCE-18001.
4. ZHP00021297, Customer complaint handling record, Q/ZHH QA-021-4.
5. ZHP00021301.
6. ZHP00021302, May 22, 2018 Email from Xaviar Tang to Yinhua Tang and Others Regarding "Unknown Peaks."
7. ZHP00021305, May 31, 2018 Email from Xaviar Tang to Kevin O'Mahony Regarding "Unknown Peaks."
8. ZHP00021306, June 4, 2018 Email from Xaviar Tang to Jannine Quinn and Kevin O'Mahony Regarding "Unknown Peaks."
9. ZHP00021307, June 6, 2018 Email from Kevin O'Mahony to Xaviar Tang Regarding "Unknown Peaks."
10. ZHP00021308, July 20, 2018 Email from Xaviar Tang to Kevin O'Mahony and Others Regarding "NDMA Impurity."
11. ZHP00021309, July 20, 2018 Letter from Minda Cai to "Whom it may concern" Regarding "NDMA Impurity."
12. ZHP00021310, Inventory Information Collection Form for Huahai Valsartan API.
13. PRINSTON00034943, 1.12.4 Request for Comments and Advice.
14. PRINSTON00036665, Testing Result of N-Nitrosodimethylamine (NDMA).
15. PRINSTON0073338, Module: 3.2.S.2.6 Manufacturing Process Development, Valsartan, USP (Process II).
16. PRINSTON00020496, 3.2.P.4.1 Specifications of Purified Water, ANDA 204821.
17. PRINSTON00020500, 3.2.P.4.1 Specifications of Magnesium Stearate, ANDA 204821.
18. PRINSTON00020504, 3.2.P.4.1 Specifications of MCC, ANDA 204821.
19. PRINSTON00020717, 3.2.P.4.1 Specifications of Colloidal Silicon Dioxide, ANDA 204821.
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21. PRINSTON00020726, 3.2.P.4.1 Specifications of Opadry II Brown, ANDA 204821.
22. PRINSTON00020730, 3.2.P.4.1 Specifications of Opadry II Yellow, ANDA 204821.
23. PRINSTON00022317, 3.2.P.4.2 Analytical procedures for Testing of Drug Substamce, ANDA 204821.
24. PRINSTON00020754, 3.2.P.5.1 Specifications, ANDA 204821.
25. PRINSTON00033450, Summary of the CBE-30 Supplement, ANDA 204821.
26. PRINSTON00039337, 3.2.P.4.1 Specifications of Crospovidone, ANDA 206083.
27. PRINSTON00039341, 3.2.P.4.1 Specifications of Colloidal Silicon Dioxide, ANDA 206083.
28. PRINSTON00039345, 3.2.P.4.1 Specifications of Purified Water, ANDA 206083.
29. PRINSTON00039349, 3.2.P.4.1 Specifications of MCC, ANDA 206083.
30. PRINSTON00039354, 3.2.P.4.1 Specifications of Magnesium Stearate, ANDA 206083.
31. PRINSTON00039359, 3.2.P.4.1 Specifications of Opadry II Pink, ANDA 206083.
32. PRINSTON00039362, 3.2.P.4.1 Specifications of Opadry II Purple, ANDA 206083.
33. PRINSTON00039378, 3.2.P.5.1 Specifications, ANDA 206083.
34. PRINSTON00079310, 2.3.S Drug Substance- Hydrochlorothiazide, ANDA 206083.
35. PRINSTON00079329, 3.2.3.S Drug Substance-Valsartan, ANDA 206083.
36. PRINSTON00078435, 3.2.S.2.3 Control Materials, DMF 020939.
37. PRINSTON00078548, 3.2.S.2.4 Control of Critical Steps and Intermediate, DMF 020939.
38. PRINSTON00078700, 3.2.S.4 Control of Drug Substance, DMF 020939.
39. PRINSTON00009342, 3.2.S.2.4 Control of Critical Steps and Intermediate, DMF 023491.
40. PRINSTON00009363, 3.2.S.2.3 Control of Materials, DMF 023491.
41. PRINSTON00009782, 3.2.S.4.1 Specification, DMF 023491.
42. PRINSTON00010529, 3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment, DMF 023491
43. PRINSTON00010648, 3.2.S.2.3 Controls of Materials, DMF 023491.
44. PRINSTON00010903, 3.2.S.2.3 Controls of Materials, DMF 023491.
45. PRINSTON00011393, 3.2.S.4.1 Specification, DMF 023491.
46. PRINSTON00017627, 3.2.S.2.4 Control of Critical Steps and Intermediate, DMF 023491.
47. PRINSTON00018280, 3.2.S.2.4 Control of Critical Steps and Intermediate, DMF 023491.
48. PRINSTON00018695, 3.2.S.4.1 Specification, DMF 023491.
49. Defendants' Letter to Plaintiffs Regarding Facility and Testing Information, dated December 2, 2019.
50. ZHP00171336, Summary of Notice of Nitrosamine Contamination and Response.
51. PRINSTON0073443, Deviation Investigation Report regarding unknown impurity (genotoxic impurity) of Valsartan API (TEA process), DCE-18003.
52. PRINSTON0075797, Investigation regarding unknown impurity (genotoxic impurity) of Valsartan API (TEA process), DCE-18003 (Version 2).

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54. PRINSTON00155822, Establishment Inspection Report 07/23/2018-08/03/2018.
55. ZHP00177912, Test result discrepancy of Valsartan batch C5271-17-288 between EU authority and that provided by Huahai, DC_E-18804.
56. ZHP01367859, ZHP Test Results.
57. ZHP00079913, DMF 23491: Response to DMF Information Request Letter (ZHP 42).
58. ZHP01843066, November 27, 2011 Change Request Form, (ZHP 195).
59. CHARLESWANG000289, June 12, 2018 Email from Charles Wang to Min Li re WHO Report (ZHP 316).
60. PRINSTON00162349, Establishment Inspection Report 07/23/2018-08/03/2018 (ZHP 312).
61. ZHP00247036, Standard Management Procedure: Change Control System.
62. CHARLESWANG000447, July 2018 Emails Between Charles Wang and Jim MacDonald (ZHP 319).
63. ZHP00037436, System QT: OQ Sample Summary Report.
64. SOLCO00028261, NDMA Test Results (ZHP 118).
65. ZHP02437848, Response to CHMP List of Outstanding Issues, dated October 31, 2018 (ZHP41).
66. ZHP01472198, NDMA Test Results (ZHP 354)
67. ZHP01472197, NDEA Test Results
68. ZHP02563814, Nitrosamine Test Results (ZHP 400)
69. ZHP00469139, Standard Management Procedure: Change Control System (ZHP 196).

Hetero Documents

1. HETERO_USA000025245, Risk Assessment Report For NDMA impurity in Valsartan tablets.

Mylan Documents

1. MYLAN-MDL2875-00029402, Sample analysis details of Valsartan (Manufacturing Processes filed in US).xlsx.
2. MYLAN-MDL2875-00037209, January 15, 2019 Letter from Shane Shupe to Kathleen Uhl Regarding ANDA 204843.
3. MYLAN-MDL2875-00033445, December 19, 2018 Letter from Beth Britton to Kathleen Uhl Regarding ANDA 078020.
4. MYLAN-MDL2875-00029533, Response to Additional Questions from FDA, dated November 30, 2018.
5. Toxicology Assessment of NDMA and NDEA in Valsartan (PL-Molnar-5).
6. MYLAN-MDL2875-00304294, Medical Risk Assessment for Amlodipine / Valsartan Tablets Valsartan Tablets and Capsules Valsartan HCTZ Tablets (PL-Molnar-6).

7. Valsartan Detail Spreadsheet (Pl-Gomas 5).
8. Triethylamine Safety Data Sheet (PL-Glover-9).
9. September 15, 2014 Email re MSDS and HSE Summary of Alkyl Amines Chemicals Ltd., products (PL-Glover-8).
10. MYLAN-MDL2875-00429120, USFDA Unit 8 Mylan Establishment Inspection Report, dated March 4, 2019.

Teva Documents

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2. TEVA-MDL2875-00004053, FDA-COPY - Valsartan and Valsartan HCTZ Finished Product list with API Lots 06 SEP 2018.xlsx.
3. TEVA-MDL2875-00005666, TEVA - Valsartan SUMMARY 7.13.2018 - FOR FDA.xlsx.
4. TEVA-MDL2875-00021547, Teva's Testing Strategy.
5. TEVA-MDL2875-00051286, Emails Between Walton Wang and Jens Nassall Regarding Audit of ZHP.
6. TEVA-MDL2875-00051288, Audit Report on ZHP (Chuannan site), Urgent audit related to Valsaran API PSD incompliance.
7. Teva Spreadsheet (Teva 230).
8. TEVA-MDL2875-00001886, September 9, 2014 Letter from Actavis to FDA re CBE notice for ZHP manufacturing process change relating to ANDA 091519.
9. TEVA-MDL2875-00013107, Jan. 9, 2015 Letter from Actavis. to FDA re CBE notice for ZHP manufacturing process change relating to ANDA 090642.
10. TEVA-MDL2875-00320639, Audit Report (Audit ID# 177267).
11. TEVA-MDL2875-00546489, February 15, 2019 Email Regarding DS Memo FDA RFI 091519 & 090642 Including Attachments.
12. TEVA-MDL2875-00048605, June 2, 2019 Email Regarding gDR# 1336473 Investigation Report Including Attachments.
13. TEVA-MDL2875-00047502, Balkanpharma Dupnitsa results for NDMA content in Valsartan tablets and Valsartan/HCT tablets.

Torrent Documents

1. TORRENT-MDL2875-00001294, Quality Information Amendment from Paul Schwartz to Dawn M. Chitty Regarding Contamination of Valsartan with NDMA.
2. TORRENT-MDL2875-00005036, Genotoxicity Statement from ZHP.
3. TORRENT-MDL2875-00504834, September 2018 Email from FDA to Torrent re: "Meeting with CDER today."
4. TORRENT-MDL2875-00131255, ZHP's August 3, 2018 Notification re NDMA in Valsartan.
5. TORRENT-MDL2875-00366172, Valsartan: Impact assessment of NDMA.
6. TORRENT-MDL2875-00135398, Valsartan API NDMA and NDEA Results.

7. TORRENT-MDL2875-00072650, August 17, 2018 Email re "Valsartan recall discussed needed."

Aurobindo Documents

1. Auro-MDL-2875-0093561, Valsartan USP and Losartan USP- API Lots Details.
2. Auro-MDL-2875-0104586, Sartan Recalls.

Regulatory Documents

1. U.S. Food & Drug Administration, Laboratory analysis of valsartan products, https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products.
2. European Medicines Agency, Assessment report, angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (Feb. 14, 2019), https://www.ema.europa.eu/en/documents/variation-report/angiotensin-ii-receptor-antagonists-sartans-article-31-referral-chmp-assessment-report_en.pdf.
3. Health Canada, Impurities found in certain angiotensin II receptor blocker (ARB) products, also known as sartans, https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/angiotensin-receptor-blocker.html.
4. U.S. Food & Drug Administration, Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) Method for the Determination of NDMA in Ranitidine Drug Substance and Drug Product (Sept. 13, 2019).
5. US FDA recommends LC-LC-HRMS for testing ranitidine products, *Reactions 1774*, p. 6 (Oct. 2019).
6. U.S. Food & Drug Administration, Statement on new testing results, including low levels of impurities in ranitidine drugs (Nov. 1, 2019), https://www.fda.gov/news-events/press-announcements/statement-new-testing-results-including-low-levels-impurities-ranitidine-drugs.
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Deposition Testimony

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2. Min Li Deposition Transcripts for April 20-22, 2021.
3. Bandar Venkata Ramarao Deposition Transcripts for April 29-30, 2021.
1. Lance R. Molnar Deposition Transcript for May 7, 2021.
2. Sanjay Singh Deposition Transcripts for May 20-21, 2021.
3. Ambati Rama Mohana Rao Deposition Transcript for April 30, 2021.
4. Daniel A. Snider Deposition Transcript for March 31, 2021.
5. Richard Derek Glover Deposition Transcripts for March 12 and April 16, 2021.
6. Antony Gomas Deposition Transcript for April 9, 2021.
7. Walt Owens Deposition Transcript for April 21, 2021.
8. Michelle Osmian Deposition Transcript for May 6, 2021.
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13. Sushil Jaiswal Deposition Transcript for June 4, 2021.
14. Dawn Chitty Deposition Transcript for May 13, 2021.

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EXHIBIT 3

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Exhibit 35

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October 31, 2022

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Dear Mr. Slater:

This report is a supplement to my report dated July 6, 2021, providing further discussion of the failure by ZHP to conduct a reasonable risk assessment of chemical reactions and necessary testing with regard to the TEA with sodium nitrite quenching process, and Zinc Chloride process, resulting in the manufacture and sale of valsartan API and finished dose contaminated with NDMA and NDEA. All opinions are stated to a reasonable degree of scientific certainty.

In summary, ZHP (and its subsidiary Shanghai Syncores that developed the zinc chloride process in the laboratory) could have and should have identified the risk of formation of nitrosamines including NDMA and NDEA, and utilized that information to test for and identify, and then prevent the nitrosamine impurities in the valsartan API and finished dose sold by ZHP. This could have and should have been done during and after development of the processes, and throughout the time that ZHP manufactured and sold the contaminated valsartan with those processes.

As stated in my July 6, 2021 report, the processes were flawed from the outset because of the inclusion of chemical reactions that could foreseeably create nitrosamines in the API. Specifically, quenching the sodium azide with sodium nitrite (nitrous acid) in the presence of the product, which led to a reaction between foreseeably created secondary amines and the nitrous acid to create NDMA/NDEA. For example, the 1978 IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, established that the reactions forming nitrosamines including NDMA and the use of mass spectrometry to identify nitrosamines were well known. In this connection, Min Li confirmed that the reaction described in the IARC monograph, "the reaction of dimethylamine hydrochloride with sodium nitrite at an acidic pH yields NDMA," is what occurred in the zinc chloride process, and this chemical reaction was known since 1865. (Min Li 4/21/21 Dep. Tr. 458:13-465:11).

In addition, ZHP has acknowledged the likely occurrence of cross-contamination of valsartan API manufactured with the zinc chloride and TEA with sodium nitrite quenching processes on shared production lines. "During the period when multiple processes co-existed in Workshop 2 and Workshop W02, equipment were cleaned as per corresponding cleaning procedure to control the residue of active substance from the previous batch when switch from one process to another. However, the residual NDMA and NDEA in the equipment after cleaning for process switch were not analyzed…Based on the analysis of the NDMA and NDEA data, the original equipment cleaning procedure applied might not be able to get rid of the NDMA and NDEA residue on the equipment completely." The Report also states that there was a risk of cross-contamination due to solvent recovery for the same reason: ZHP was not looking for NDMA or NDEA because they failed to perform a straightforward assessment of the chemistry. (ZHP Deviation Investigation Report dated November 5, 2018 (DC-18003, PRINSTON0075797, at 126-130). Min Li of ZHP confirmed: "the DEA [diethylamine] is a typical process impurity of TEA, so DEA would also, yeah, would react with the nitrous acid to perform NDEA." With regard to NDMA, "in some of the TEA raw material it may contain a trace amount of, you know, of dimethylamine, okay, so that's one root cause…for some of the, you know, product, they were manufactured, you know, using the share line, you know, with the zinc chloride valsartan." (Min Li 4/20/21 Dep. Tr. 77:8-80:16). Varied NDMA levels were found in the valsartan API produced in the East and West zones at Chuannan, per the TEA process DIR. ZHP identified factors that would impact the NDMA levels. This includes, "number 1, temperature when adding sodium nitrite; number 2, charging speed of hydrochloride acid; number 3, ph control at the end; and number 4, aqueous phased separation time during quenching." In this connection, ZHP recognized that there was "a lack of detailed description in the production processes." ZHP further stated, "Due to the inaccurate description of some of the parameters in the process, there might be likelihood of fluctuation between different workshops or different batches manufactured in the same workshop, which eventually led to the difference in the amount of residual impurities…the residual amounts of NDMA in valsartan API batches." (Peng Dong 4/2/21 Dep. Tr., 536:7-543:2). Assessment and understanding of the potential chemical reactions in each process would have required testing for NDMA and NDEA of each batch of drug product manufactured with both processes, whether due to the process or cross-contamination, and would have shown the presence of NDMA and NDEA in each batch, as applicable.

The readily available scientific knowledge and testing should have been applied to identify the NDMA and NDEA even after the processes were adopted. This should have been apparent to any organic chemist involved in the development or assessment of these processes. Once ZHP went forward with the processes after having failed to detect and prevent the nitrosamine contamination during the development of the processes, ZHP could have and should have identified the nitrosamine impurities before selling the API or finished dose with NDMA/NDEA impurities. The same scientific knowledge and principles I have discussed with regard to the development of the processes was equally available and could and should have been applied when the product was manufactured for sale. This would have been as easy as adding appropriate testing for NDMA and NDEA to the specifications, and

testing each batch of API and finished dose accordingly. The result would have been detection of the nitrosamines.

ZHP has stated that the detection of the nitrosamines was not possible since they had no knowledge of the potential or actual presence of the nitrosamines and did not possess the technological ability to identify these impurities. I disagree. The deposition testimony provides context for this issue. For example:

Jun Du testified with regard to the August 26, 2018 letter written by ZHP (and signed by him) to the FDA, stating in part that, "it is not the residual DMF that reacts with nitrous acid of the next step, but rather it is the trace amount of dimethylamine, an impurity/degradant of DMF that reacts with nitrous acid to form NDMA, which adds a further dimension over the current thinking, logic and strategy for the evaluation of potential genotoxic impurities. It is this extra dimension over the current industry practice that obscured us from foreseeing this impurity during the process change from triethylamine process to zinc chloride process." (Jun Du 5/28/21 Dep. Tr. 232:18-234:6).

In the November 28, 2018 FDA Warning Letter to ZHP, the FDA explicitly, and correctly disagreed with ZHP's position that this could not be known, "You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change….Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and that your process development study was adequate. We disagree. We remind you that common industry practice may not always be consistent with cGMP requirements and that you are responsible for the quality of drugs you produce." (ZHP01344159 (ZHP 213)). Dr. Li and Mr. Du agreed with the FDA that ZHP was "responsible for the quality of the drugs" produced by ZHP. (Min Li 4/21/21 Dep. Tr., 426:8-427:5, 430:11-434:10) (Jun Du 5/28/21 Dep. Tr. 247:17-250:22).

The FDA also stated in the Warning Letter, "You are responsible for developing and using suitable methods to detect impurities when developing, and making changes to your manufacturing processes. If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients." (Jun Du 5/28/21 Dep. Tr. 237:18-243:20). As stated in my prior report, the knowledge, technology, and methods to identify the NDMA and NDEA were readily available and should have been applied to identify the contamination, and this could and should have been done during development of the processes, and then again once ZHP began to manufacture valsartan with those processes for sale.

In this context, a draft of ZHP's deviation investigation report titled "Investigation Regarding an Unknown Impurity (Genotoxic Impurity)" stated that, "Due to insufficient extent and depth of process research at the early stage, as well as insufficient study and understanding of potential genotoxic impurities, only side reaction product and degradation

products were studied, and was unaware of the further reaction between degradation products and raw material." (Min Li 4/22/21 Dep. Tr. 528:5-531:4). This accurately describes the inadequate scientific risk assessment performed by ZHP, since the chemical reactions and means to test for the foreseeable creation of nitrosamines were well known and available. Scientifically reasonable process research, study and understanding of potential genotoxic impurities, would have resulted in recognition of the risk of creating the nitrosamine impurities, and testing that would have demonstrated the presence of these impurities. I know this from my own personal experience utilizing mass spectrometry to identify nitrosamines including NDMA beginning long before development of these processes in 2011, and the scientific literature including what is identified here and in my prior report, as well as in questioning of ZHP witnesses.

The focus on nitrosamines as potential human carcinogens began after the first demonstration of the carcinogenicity of dimethylnitrosamine in 1956 as outlined in my previous reports. The first report of nitrosamine contamination of food was published in 1968, and the first definitive evidence for the presence of dimethylnitrosamine in meat products in 1972.[1] This stimulated the development of reliable analytical methods for nitrosamines, layered on the existing knowledge base. A review published in 1976 notes the initial development of methods for the analysis of trace amounts of nitrosamines: "there is now no doubt that these compounds do occur in trace amounts in various environmental situations."[2] It goes on: "Recently a better standardization of the methodology, using gas-liquid chromatography and mass spectrometry, has yielded more reliable identification of the nitrosamines."

Fine et al reported the development of a highly sensitive and reliable nitrosamine-selective detector (the Thermal Energy Analyser, or TEA) in 1975.[3] Coupling of TEA to gas chromatography (GC-TEA) became the standard method for analysis of ultra-trace levels of nitrosamines. Thousands of products including pharmaceuticals were reliably analyzed and shown to contain trace amounts of nitrosamines (reviewed in Forman, D. and Shuker, D. Nitrate, nitrite and nitroso compounds in human cancer, *Cancer Surveys* 8: 205-487 (1989)), leading to international concern, further analyses, and mitigation efforts. Ultimately with the development of improved gas chromatography-mass spectrometry (GC-MS) methods and the wide availability of this instrumentation by the early 1980s, GC-TEA gave way to GC-MS which was even more reliable because of its ability to directly determine structural information from fragmentation patterns, information that was not available by GC-TEA. A review published in 1989 summarizes hundreds of analyses of nitrosamines in food.[4]

Thus, there is no doubt that the necessary technology and highly reliable methods for the analysis of nitrosamines in various settings were available from the 1970s. More recent analyses have confirmed the earlier data.

The international concern about the presence of these carcinogens in various settings gave rise to the widely attended and recognized International Agency for Research on Cancer conferences on nitrosamines which were held at various locations in the world from 1976-

1991. These meetings produced a series of books describing the research discussed at the meetings.[5]

In summary, nitrosamine contamination of food, drugs, and other products, and the reliable analytical methods to detect nitrosamines, have been known since the 1970s. Routes of formation of nitrosamines under various conditions have been extensively described in numerous publications and textbooks. Chemists using processes which involve the presence of nitrite and secondary amines should absolutely be aware of this huge body of literature, and utilize the widely available technology and methods to identify the nitrosamines resulting from these processes.

ZHP's witnesses acknowledged in their depositions that the chemical reactions were known and that mass spectrometry was available to identify nitrosamines starting before these processes were even developed. Dr. Li ultimately agreed that "the technology and the methodology was clearly available to identify the NDMA," as long as you "know what to look for" based on a risk assessment – which he confirmed is an ongoing process for the lifecycle of the drug. (Min Li 4/20/21 Dep. Tr., 230:9-19, 233:10-18).

Eric Gu also confirmed in his deposition that the 1978 IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans" stated in part: "It has been known since 1865 that the reaction of dimethylamine hydrochloride with sodium nitrite at an acidic pH yields NDMA." (Eric Gu 4/5/21 Dep. Tr., 65:3-65:24). Mr. Gu was shown a 2009 article published in the scientific journal Tetrahedron Letters, titled: DMF, Much More Than a Solvent. The article states that "DMF decomposes slightly at its boiling point to afford dimethylamine and carbon monoxide, this reaction occurring even at room temperature in the presence of acidic or basic materials..." He agreed that DMF could decompose to yield dimethylamine, and this was known in the scientific community. (Eric Gu 4/5/21 Dep. Tr., 172:13-174:9, 183:12-21).

Min Li was shown scientific literature identifying the risk of formation of nitrosamines during his deposition. This includes a textbook first published in 1996 titled, Purification of Laboratory Chemicals, which stated that DMF could decompose at its boiling point to yield dimethylamine. (Min Li 4/21/21 Dep. Tr. 391:13-395:5). Another 2009 scientific article titled "N.N-Dimethylformamide: much more than a solvent," also stated that DMF could decompose to produce dimethylamine, and this article cited a textbook published in 1966. (Min Li 4/21/21 Dep. Tr. 411:19-413:22). In addition, an article published in 2010 by a group from Beijing University of Technology in the Journal of Physical Chemistry titled "Theoretical Investigation of N-Nitrosdimethylamine Formation from Nitrosation of Triethylamine," described the formation of NDMA from the reaction of dimethylamine and nitrous acid. This is what occurred here with the zinc chloride process. (Min Li 4/21/21 Dep. Tr. 414:2-416:12). Dr. Li also stated that this was the reaction that occurred in the zinc chloride process: "the zinc chloride process for the formation of NDMA, you know, was also under the acidic, you know, pH. So, yes, so from that perspective, yeah, they are consistent." He also confirmed that in 2011, "scientists would be aware of and have available to them" this information, as well as

the known availability and use of mass spectrometry to test for potential nitrosamines, as stated in the 1978 Monograph, "The principal techniques employed for the analysis of volatile N-nitrosamines [including NDMA] have been described in a recent publication…The relative merits of high- and low-resolution mass spectrometry are discussed, since use of mass spectrometry as a confirmatory technique is particularly important." (Min Li 4/21/21 Dep. Tr. 458:13-465:11). The literature discussed with the ZHP witnesses provides useful examples and is representative of information that was well known in the scientific literature and scientific community prior to and after the 2011 development of these processes.

The identification of the NDMA and NDEA would have been straightforward to anyone who was familiar with the chemical reactions in the manufacturing process, utilizing mass spectrometry. The location of the NDMA peak found on the chromatograms for the zinc chloride process has been identified by ZHP. For example, Min Li testified that there was a "little peak after the toluene peak" and stated, "And then in the sample injection, this peak turns out, if I remember correctly, to be n-butyl acetate, okay? So that's the peak - - that's the peak, you know, eluting after the toluene peak. Okay. So NDMA would elute on the shoulder, or sometimes may even completely co-elute with this peak." (Min Li 4/20/21 Dep. Tr. 25:16-28:22.). In addition, Qiangming Li confirmed that "[w]hen we used GC-FID for the testing, regarding the peak that appeared after toluene, the response of NDMA was pretty low." (Qiangming Li 4/14/2021 Dep. Tr. 168:17-20). The point is that taking into account the potential creation of nitrosamines should have led to the use of the GC-MS technology to identify the NDMA and NDEA.

A series of customer complaints was received by ZHP with regard to the unknown, or aberrant peaks on the chromatography. This included:

1. Ranbaxy/SunPharma on September 30, 2014 (Qiangming Li 4/14/2021 Dep. Tr. 130:7-170:11; ZHP01748896 (ZHP 260)).

2. Shanghai Pharmtech on November 20, 2014 (*Id.* at 177:22-199:20; ZHP01748905 (ZHP 264)).

3. SunPharma on November 17, 2016 (Qiangming Li 4/15/2021 Dep. Tr. 290:16-318:10; ZHP00405069 (ZHP 277); ZHP01313866 (ZHP 278)).

4. Vertex on December 21, 2016 (Qiangming Li 4/14/2021 Dep. Tr. 204:11-214:17; ZHP02630924 (ZHP 265); ZHP02630926 (ZHP 266).

5. Glenmark on December 29, 2016 (Qiangming Li 4/15/2021 Dep. Tr. 254:22-290:4; ZHP00496153 (ZHP 271); ZHP00496155 (ZHP 272); ZHP02118712 (ZHP 273)).

6. Aurobindo on August 23, 2017 (*Id.* at 343:21-372:9; ZHP02094739 (ZHP 281)).

7. Novartis on May 22, 2018 (*Id.* at 386:17-466:17; ZHP00405021 (ZHP 284)).

Testing with the available technology would have identified the NDMA and NDEA at every point during the period when these processes were used to manufacture the valsartan. Novartis did what ZHP should have done. Novartis investigated the unknown peaks to determine what was causing them, and identified the NDMA in ZHP API manufactured with the Zinc Chloride process. Of note, Novartis inquired of ZHP as to whether DMF was utilized in the zinc chloride process on June 7, 2018, as part of its investigation. (ZHP01390017). This was relevant information to be taken into account by anyone assessing the cause of the unknown peaks since dimethylamine was the degradation/decomposition product of DMF that then reacted with the nitrous acid to form NDMA. ZHP simply ignored or didn't understand this basic chemistry. ZHP failed to perform the same analysis despite knowing the details of the manufacturing process, and this illustrates the inadequacy of ZHP's risk assessment from the perspective of organic chemistry.

I have reviewed chromatograms for the zinc chloride process. The NDMA peak would not have been identifiable as NDMA on the gas chromatography alone, but as stated above if ZHP had been diligent and conducted a scientifically reasonable assessment, they would have recognized the need to test for NDMA, and they could have used the available technology to identify the NDMA peak. We have examples of the results that would have been obtained in the documentation of the testing performed after the disclosure of the NDMA in June, 2018. The September 1, 2018 ZHP Response to DMF Information Request Letter provides a series of chromatograms showing the methods used, and the identification of the NDMA peak. (ZHP00079913). There was nothing complex or difficult about what was done once they were looking for the NDMA (and ultimately NDEA). In another example, the July 20, 2018 Deviation Investigation Report titled: Investigation regarding a Suspected Genotoxic Impurity of Valsartan (ZHP00004363) contains images of the June 6, 2018 email and attachments from Kevin O'Mahony to Xavier and others at ZHP. The chromatograms show the NDMA peak, and the method used to identify the peak, (ZHP00004399-4402). This should have been identified from the outset and at every other point moving forward, including when Novartis and other customers submitted complaints and inquiries regarding unknown peaks, as listed above. In this context, the European authority documented that Novartis had shared its analytical method with ZHP in July, 2017, in rebutting ZHP's argument that it did not have that information until June 2018. (ZHP01862681 (ZHP 232)). Of note, and perhaps not a coincidence, the July 27, 2017 email written by Jinsheng Lin, Ph.D. confirming that there was NDMA in ZHP's valsartan API, caused by the quenching with sodium nitrite, was written during the same month.

The same analysis applies to the NDEA in the valsartan. For example, August, 2018 testing performed by ZHP shows the NDEA peak identified. (ZHP02733180).

When asked why Novartis discovered that an unknown peak was due to NDMA before ZHP, he acknowledged that ZHP was required to investigate the peak, but could not give an explanation, "it was not so easy to detect" and "it's quite a challenging work." (Eric Gu 4/5/21

Dep. Tr., 210:24-219:5, 236:24-237:8). As set forth above, identification was quite feasible and should have been accomplished from the start of development of these processes, through the entire time that the drug products were manufactured and sold. This could have been done at any point, and seeming to contradict ZHP's position that it did not know, the July 27, 2017 email accurately describes the presence of the NDMA and the root cause of quenching with sodium nitrite.

Mr. Gu was questioned about the aberrant/unknown peaks. He had no reasonable explanation for why, despite every batch demonstrating the "NDMA peak just after the Toluene peak on the chromatograms. . . nobody at ZHP realized that it needed to be tested and identified." Mr. Gu admitted that ZHP was aware of these peaks and "did whatever they can," however, "They are struggling, I guess, in the past." (Eric Gu 4/6/21 Dep. Tr., 333:21-335:19). Mr. Gu was not aware that ZHP customer Sun Pharmaceuticals complained of unknown peaks in November 2016, and was not aware that, according to the European Medicines Agency, ZHP did not directly compare the unknown peaks observed by Novartis to ZHP's own gas chromatography. Nor was he aware that Novartis had shared its GC-FID method for evaluating chromatogram peaks with ZHP in July 2017. (Eric Gu 4/5/21 Dep. Tr., 240:3-243:18).

To be clear, the pathway to identification of the NDMA and NDEA impurities continued to be straightforward after the valsartan containing NDMA and NDEA began to be marketed. ZHP could have and should have taken the steps described above from the time they began to sell the valsartan containing NDMA and NDEA until it was discovered by Novartis, with the aid of an outside laboratory in June 2018. The necessary information and technology was readily available the entire time.

In addition to the ease in detecting the NDMA and NDEA with available testing, if ZHP still determined to go forward with these processes, the simple step of extracting the product prior to the quenching could have been taken to prevent the NDMA (and NDEA in the TEA with sodium nitrite process) formed in the zinc chloride process during quenching of the sodium azide from contaminating the drug product. ZHP stated in one document that, "any formation of NDMA will not be carried over into the product," and, "This approach can be done without any change of manufacturing process." July 1, 2018 Investigation of the Source of this Impurity (NDMA) (ZHP01495188). ZHP also provided a detailed analysis at pages 29-35 of 236 of the November 5, 2018 Deviation Investigation Report (PRINSTON0075797), indicating: "After optimization, the ROS remains the same, the product in Valsartan Crude Step (Step 4) is separated before the addition of NaNO2 (and the subsequent addition of Hcl)…Therefore, the product in the organic phase has no chance to be contaminated by NDMA." This would not have changed the manufacturing process for the drug product or route of synthesis as recognized by ZHP, and would not have negatively impacted or introduced any risk to the identity, quality, purity, strength, or stability of the drug products, since the drug product would have been separated from and not been exposed to contamination by the genotoxic impurities created during the quenching step. The same could have been done with the TEA with sodium nitrite quenching process. In the alternative,

ZHP could simply have gone back to the original process that did not involve sodium nitrite quenching, as "no NDMA or NDEA will be formed in Tin process." (November 5, 2018 Deviation Investigation Report, at 68 of 236, PRINSTON0075870).

Eric Gu confirmed that ZHP modified the zinc chloride manufacturing process after the FDA became aware of the NDMA, and agreed that ZHP's, "solution was to quench the azide separate from the product so it wouldn't become contaminated with the NDMA," and, "GC-MS would be used to evaluate all peaks to make sure that they were not genotoxic impurities that needed to be controlled out of the product." (Eric Gu 4/6/21 Dep. Tr., 455:1-458:15). If the solvents presenting the risk of secondary amines and sodium nitrite quenching were to be used, this would have prevented contamination of the drug product, and this testing would have confirmed the lack of NDMA or NDEA; this was absolutely feasible and could and should have been done from development through the entire course of the manufacturing of the drug product if the same solvents and chemicals were to be used in the process.

The ZHP API and Finished Dose Nitrosamine Levels
Are Materially the Same and All Exceed the FDA Levels

Minli Zhang—ZHP's Director of Finished Dose Formulation Quality—testified that ZHP determined its APIs' nitrosamines carried over to the finished dose. (3/26/2021 Minli Zhang Dep. Tr. 509:15-17, 518:18-519:3). Ms. Zhang explained:

> In our investigation report, we compared the NDMA level in the API and the NDMA level in the finished dose products, and we found the results basically matched each other. Therefore, we decided not to test the NDMA level in the finished dose products anymore.
>
> We could simply calculate based on the NDMA level in the API, as well as the amount of API used, to come up with a probable level of NDMA in the finished dose products.

(*Id.* at 521:8-19). This is the chart from the deviation investigation report:

In order to qualify the impurity relationship between the dosage form and API, some batches of API and corresponding dosage form were choose at random to test this impurity by Quality Research Department (QR), the testing result is as below:

表 1：制剂成品及对应 API 批次检测结果列表

Table 1: testing result between dosage form batches and corresponding API

序号 SN	产品名称 Product Name	产品批号 Batch No.	产品规格 Strength (mg)	API 厂家批号 Vendor batch No. Of API	API 结果 Result for API	制剂结果 Result for dosage form
					NDMA 含量(ppm) Assay of NDMA (ppm)	
1.	缬沙坦片 USP Valsartan Tablets USP	341A18007	40	C5523-17-382	81.4	83.1
2.	缬沙坦片 USP Valsartan Tablets USP	342B17012	80	C5523-17-190	101.9	101.0
				C5523-17-191	101.7	
3.	缬沙坦片 USP Valsartan Tablets USP	343G17002	160	C5355-17-132	120.0	110.3
				C5355-17-133	104.5	
4.	缬沙坦片 USP Valsartan Tablets USP	344B17071	320	C5355-17-131	119.3	123.2
				C5355-17-132	120.0	
5.	缬沙坦氢氯噻嗪片 USP Valsartan HCTZ Tablets USP	609B18003	80/25	D5191-16-133	3.4	2.9
6.	缬沙坦氢氯噻嗪片 USP Valsartan HCTZ Tablets USP	611B17003	320/25	D5191-16-027	27.7	31.3
7.	缬沙坦氢氯噻嗪片 USP Valsartan HCTZ Tablets USP	611B17007	320/25	D5191-15-149	7.9	6.4

从上表数据分析，制剂产品与 API 的检测结果的差值接近(0.5~9.7ppm)。

Based on analysis above, the testing difference value of API and dosage form is almost the same (0.5-9.7ppm)

(ZHP00683571, 683578). As a result, ZHP stopped testing FD and blended the API levels to get the FD ones. (*Id.* at 520:22-523:19, 525:12-22 (discussing ZHP 189)). Hai Wang—the President of Solco—confirmed that the API and FD contained the same levels of nitrosamines. (3/10/2021 Hai Wang Dep. Tr., 116:3-118:23, 144:15-147:1). Prinston explicitly informed the FDA that "[i]t is confirmed that NDMA has been present in Valsartan drug substance (API) batches and carried to the drug product Valsartan," relying on the same test results as shown in the above chart. (PRINSTON00249966, 249967; ZHP00099424, 99441-42). ZHP concluded this analysis applied to NDEA as well. (PRINSTON0075797, 75977 (stating: "According to the previous raw material investigation, i.e. presence of diethylamine impurities in triethylamine hydrochloride, combined with the formation mechanism of NDEA, it should be the nitrosation of diethylamine impurities (in triethylamine hydrochloride) by nitrite to produce NDEA impurities, which is carried over into crude products, and finally remain in valsartan finished products.")).

As set forth in my July 6, 2021 report, testing by Teva and Torrent of its finished dose products manufactured using the ZHP contaminated valsartan API also established that the

levels of NDMA and NDEA all exceeded the limits set by the FDA. (TEVA-MDL2875-00546489 (TEVA 155); TORRENT-MDL2875-00005092; TORRENT-MDL2875-00369262; TORRENT-MDL2875-00072916; TORRENT-MDL2875-00366172).

Conclusion

The unreasonably dangerous contamination of valsartan drug products with NDMA and NDEA was easily avoidable, based on prevailing scientific knowledge and technology that existed before, during, and after the development and then commercial use of the zinc chloride and TEA with sodium nitrite quenching processes. The available knowledge and technology should have been applied to add straightforward testing for NDMA and NDEA of each batch of API and finished dose manufactured using the API manufactured with these processes, which would have revealed the presence of the NDMA and NDEA. The contamination of the drug product could have been prevented by extracting the product before quenching the sodium azide.

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EXHIBIT A
Supplemental List of Materials Reviewed

ZHP Documents

1. PRINSTON00249966, August 27, 2018 Letter from Prinston to the FDA regarding ANDA 206083.
2. ZHP02326538 (ZHP 189).
3. ZHP00662283, Draft Investigation regarding an unknown impurity (Genotoxic Impurity) (ZHO 212).
4. ZHP01862672, Final GMP Inspection Report (ZHP 232).
5. ZHP01748896, Email Chain between ZHP and Ranbaxy (ZHP 260).
6. ZHP01748905, Email Chain between ZHP and Shanghai Pharmttech Co. Ltd. (ZHP 264).
7. ZHP02630924, Email Chain regarding Vertex (ZHP 265).
8. ZHP02630926, Chronology regarding Vertex (ZHP 266),
9. ZHP00496153, Email Chain regarding Glenmark (ZHP 271).
10. ZHP00496155, Chronology regarding Glenmark (ZHP 272).
11. ZHP02118712, Email Chain between ZHP and Glenmark (ZHP 273).
12. ZHP00405069, Email Chain between ZHP and Sun Pharmaceutical Industries Ltd. (ZHP 277).
13. ZHP01313866, Chromatograms from Sun Pharmaceutical Industries Ltd. (ZHP 278).
14. ZHP02094739, Email Chain between ZHP and Aurobindo (ZHP 281).
15. ZHP00405021, Email Chain between ZHP and Novartis (ZHP 284).
16. ZHP00099424, Meeting Information Package from Prinston regarding ANDA 204821.
17. ZHP01390017, Email Chain Between ZHP and Novartis.
18. ZHP01495187, Investigation of the Source of this Impurity (NDMA).
19. ZHP01344159, November 29, 2018 Warning Letter from the FDA to ZHP (ZHP 213).
20. ZHP01495186, July 1, 2018 Email Enclosing ZHP01495187, Investigation of the Source of this Impurity (NDMA).
21. ZHP02733180, Chromatogram and Results for NDEA in ZHP's valsartan
22. PRINSTON00002249, 1-2 Annex-3 NDMA for TEA Process by GC-MS
23. ZHP02365339, Valsartan Chromatograms
24. ZHP02364173, NDMA and NDEA test results for all batches of Valsartan in USDMF grade
25. ZHP00011368, Certificate of analysis for D5191-14-157M
26. ZHP00344175, Summary of Unspecified Peaks in Residual Solvents Method of Valsartan
27. ZHP00476862, Valsartan Impurities Profile Analysis Report (ZHP 220)

28. ZHP00021455, Study Report of Unknown Peak in Residual Solvent of Valsartan
29. ZHP01870977, Study Report of Unknown Peak in Residual Solvent of Valsartan
30. ZHP02214602-71, Novartis Documents
31. ZHP02633528-ZHP02633538
32. ZHP00405024-ZHP00405068
33. ZHP00380568-ZHP00380591
34. ZHP01748896-ZHP01748899-ZHP1748899 (ZHP 260)
35. ZHP00405069-ZHP00405070 (ZHP 277)
36. ZHP01320376-ZHP01320392 (ZHP 280)
37. ZHP00405021-ZHP00405023 (ZHP 284)
38. ZHP00359796-ZHP00359822 (ZHP 288)
39. ZHP02135008-ZHP02135025 (ZHP 289)
40. ZHP02173090-ZHP00371269 (ZHP 290)

Torrent Documents

1. TORRENT-MDL2875-00072916, Details of Finished good batches (USA market) manufactured at indrad with Huahai API having old ROS.
2. TORRENT-MDL2875-00366172, Valsartan: Impact assessment of NDMA.
3. TORRENT-MDL2875-00369262, Test Results
4. TORRENT-MDL2875-00005092, Details of Finished good batches manufactured at indrad with Huahai API having old ROS.

Deposition Testimony

1. Minli Zhang Deposition Transcript for March 22-26, 2021.
2. Eric Gu Deposition Transcript for April 5-6, 2021.
3. Qiangming Li Deposition Transcript for April 13-16, 2021.
4. Jun Du Deposition Transcript for May 27,-28, 2021.

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